DECLARATION UNDER 37 C.F.R. §1.132
Examining Group 1614
Patent Application
Docket No. UF-260XC1
Serial No. 09/997,447

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Phyllis G. Spivack
Art Unit	:	1614
Applicants	:	Nathan Andrew Shapira, Mary Catherine Lessig, Daniel John Driscoll
Serial No.	:	09/997,447
Filed	:	November 30, 2001
Conf. No.	:	3440
For	:	Treatments for Neurogenetic Disorders, Impulse Control Disorders, and Wound Healing

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION OF GREGORY W. SCHULTZ, PH.D. UNDER 37 C.F.R. §1.132

Sir:

I, Gregory W. Schultz, Ph.D., hereby declare:

THAT, I have received the following degrees:

Doctor of Philosophy 1976 Oklahoma State University, Stillwater, Oklahoma

Bachelor of Science 1971 Oklahoma State University, Stillwater, Oklahoma

THAT, I have been employed professionally as follows:

Academic Appointments

1989-present	Professor of Obstetrics/Gynecology, University of Florida, College of Medicine, Gainesville, Florida
1985-1989	Associate Professor of Ophthalmology, University of Louisville School of Medicine, Louisville, Kentucky
1985-1989	Associate Professor of Biochemistry, University of Louisville School of Medicine, Louisville, Kentucky
1979-1985	Assistant Professor of Biochemistry, University of Louisville School of Medicine, Louisville, Kentucky
1976-1979	Postdoctoral Research Associate, Yale University School of Medicine, New Haven, Connecticut
1974-1976	Graduate Student, Kansas University Medical Center, Kansas City, Kansas
1971-1974	Graduate Student, Oklahoma State University, Stillwater, Oklahoma
1967-1971	Undergraduate in Biochemistry, Oklahoma State University, Stillwater, Oklahoma

THAT, I am the Director of the Institute for Wound Research at the University of Florida and that my research focuses on the role of growth factors, cytokines and proteases in normal and chronic wound healing in the skin and in the eye. I have published over 170 research papers, chapters and review articles (a sampling of which is included on the attached Curriculum Vitae). These papers have been cited more than 4,400 times and I have multiple patents in the areas of wound healing. I was President of the Wound Healing Society from 1999-2001.

THAT, through my years of research, I have kept up to date on the technical literature and maintained contact with experts in the field by participating in professional meetings and seminars, and by direct personal contact. As a result, I am familiar with the general level of skill of those working in the field of wound healing;

THAT, I have studied application Serial No. 09/997,447, filed on November 30, 2001, the Office Actions which have been issued during prosecution of this application, the references cited in these Office Actions, and the responses which have been filed on the behalf of Applicants. Thus, being duly qualified, I declare as follows:

1. I have reviewed the disclosure of Blake *et al.* (International Application PCT /GB99/02606; International Publication No. WO 00/10610) and cannot agree with the assertion of the Patent Office that this reference would motivate one skilled in the art to use topiramate to promote wound healing. The reference is directed to the manufacture and use of bioreductive conjugates of known therapeutic agents for use in the treatment of conditions or diseases for which the therapeutic agent is recognized to be useful.

While the reference addresses or claims medicaments for "use in the healing of wounds or the treatment of fibrotic disorders", the therapeutic agents indicated as being useful in this regard are limited to growth factor neutralizing agents or agents specific against only fibrotic growth factors (see claims 2 and 3); the reference specifically speaks to neutralizing growth factors, interleukins, or other agents that are typically associated with inducing fibrosis or scarring. Specific examples of such agents that are provided in the description of Blake *et al.* are TGF-β1; TGF-β2; PDGF; IFNγ; IL-1; TGF-β3; FGF-1; FGF-2; IL-4; IL-10; betaglycan; inhibitors of: IFN-γ, at least one integrin receptor, at least one convertase enzyme, or IL-6; stimulators of: IFN-γ or activin and/or inhibin; agents that modulate actin assembly and organization, latency associated peptide; insulin like growth factor II; or compounds that influence the sex hormone system (see claims 4-21 and the description of the embodiment directed to wound healing at pages 4-14). Indeed, the description at pages 4-14 repeatedly states that the embodiments discussed on these pages are directed to wound healing (see, for example, page 7, paragraph 5; page 8, paragraphs 1 and 4; page 9, paragraphs 2 and 6; page 10, paragraph 2; page 11, paragraphs 3 and 7; page 12, paragraphs 2 and 5; page 13, paragraph 4; and page 14, paragraphs 1 and 4).

I note that topiramate is absent from the listing of agents for use in promoting the healing of wounds or the treatment of fibrotic disorders. This is not surprising as, to the best of my knowledge, there was no recognition (nor was it suspected) that topiramate had such an activity prior to the filing date of this patent application. As the Patent Office may be aware, topiramate is a drug recommended for the treatment of epilepsy (as is disclosed in the description of Blake *et al.* at page 15, paragraph 1 and the Physician's Desk Reference, a copy of which is appended hereto).

As one skilled in the art, I would not have been motivated to use topiramate for the treatment of wounds or for promoting wound healing in view of the teachings of Blake *et al.* nor would the use of topiramate for promoting wound healing be suggested to me in view of the teachings of the reference. Furthermore, as one skilled in the art, I would not, and could not, reasonably infer that the reference teaches or suggests or motivates one to use topiramate for promoting wound healing as is argued by the Patent Office.

2. As indicated above, there was, to the best of my knowledge, no recognition in the art that topiramate was useful for promoting wound healing in individuals to whom topiramate was administered and, based upon my experience in the field or wound healing, I would not have expected topiramate to provide therapeutic benefit in promoting wound healing.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: Gregory W. Schultz, Ph.D. Date: 9-23-04

Attachments: Physician's Desk Reference (2000)
Curriculum Vitae

CURRICULUM VITAE

Gregory Scott Schultz

Business Address
Department of Ob/Gyn
University of Florida
College of Medicine
Box 100294, J. H. Miller Health Center
1600 SW Archer Road
Gainesville, Florida 32610
Phone: (352)-392-4060
FAX: (352)-392-6994
Cell: (352)-538-1951
E-Mail: SCHULTZG@OBGYN.UFL.EDU

Education

1971	B.S.	Honors Program in Biochemistry, Oklahoma State University, Stillwater, Oklahoma
1976	Ph.D.	Biochemistry, Oklahoma State University, Stillwater, Oklahoma Dissertation Advisor: Dr. Kurt Ebner, Regent's Professor
1979	Postdoctoral Fellow	Cell Biology, Yale University, New Haven, CT Advisor: Dr. James D. Jamieson, Professor and Chairman

Academic Appointments

1989-present	Professor of Obstetrics/Gynecology, University of Florida, College of Medicine
1985-1989	Associate Professor of Ophthalmology, University of Louisville School of Medicine
1985-1989	Associate Professor of Biochemistry, University of Louisville School of Medicine
1979-1985	Assistant Professor of Biochemistry, University of Louisville School of Medicine
1976-1979	Postdoctoral Research Associate with Dr. James D. Jamieson, Professor of Cell Biology, Yale University School of Medicine
1974-1976	Graduate student with Dr. Kurt Ebner, Professor and Chairman Department of Biochemistry, Kansas University Medical Center, Kansas City, Kansas
1971-1974	Graduate student with Dr. Kurt Ebner, Regents Professor of Biochemistry Oklahoma State University, Stillwater, Oklahoma
1967-1971	Undergraduate in Biochemistry Oklahoma State University, Stillwater, Oklahoma

Professional Societies
Phi Kappa Phi
American Society for Biochemistry and Molecular Biology
The Wound Healing Society
Association for Research in Vision and Ophthalmology

Awards and Honors
Medicinae Doctorem (honoris causa) awarded by University of Linköping, Sweden, May 1996
Everett Kinsey Lecturer of the Contact Lens Association of Ophthalmologist, January 1997
1st Ethicon Endo-Surgery Plenary Lectureship of the American Society for Reproductive Medicine, October, 1997
University of Florida Bank Research Award, 1997
Professorial Excellence Program Award, University of Florida, 1998
President of the Wound Healing Society, 1999-2001
Sustained Excellence Professors Award, University of Florida, 2001
Thygeson Lecturer of the Ocular Microbiology and Immunology Group, 2002

REFEREED PUBLICATIONS

NOTE: SCIENCE CITATION INDEX LIST 4,500 CUMULATIVE CITATIONS TO DR. SCHULTZ'S REFEREED PUBLICATIONS IN JANUARY 2002: 24 PUBLICATIONS WITH >50 CITATIONS, 10 PUBLICATIONS >100 CITATIONS, 7 PUBLICATIONS WITH >150 CITATIONS AND 3 PUBLICATIONS WITH >250 CITATIONS

1. D.W. Wesson, M.P. Popp, L. Liu, G.S. Schultz, M.B. Sherwood. Microarray Analysis of the Failure of Filtering Blebs in a Rat Model of Glaucoma Filtering Surgery. **Invest Ophthalmol Vis Sci,** in press.
2. S.A. Berceli, Z. Jiang, N.V. Klingman, C.L. Pfahnl, Z.S. Abouhamze, C.D. Frase, G.S. Schultz, C.K. Ozaki. Differential Expression and Activity of MMPs during Flow–Modulated Vein Graft Remodeling. **J Vasc Surg**, 39:1084-1090, 2004.
3. T.D. Blalock, R. Yuan, A.S. Lewin, G.S. Schultz. Hammerhead Ribozyme Targeting Connective Tissue Growth Factor mRNA Blocks Transforming Growth Factor-Beta Mediated Cell Proliferation. **Exp Eye Res**, 78:1127-1136, 2004.
4. R.J. Freezor, H.N. Paddock, H.V. Baker, J.C. Varela, L.L. Moldawer, G.S. Schultz, D.W. Mozingo. Temporal Patterns of Gene Expression in Murine Dermal Burn Wound Healing. **Physiol Genomics**, 16:341-348, 2004.
5. Q. Garrett, T.D. Blalock, P.T. Khaw, G.S. Schultz, G.R. Grotendorst, J.T. Daniels. CTGF is Involved in TGF-β1-Stimulation of Myofibroblast Differentiation and Collagen Matrix Contraction in the Presence of Mechanical Stress, **Invest Ophthalmol Vis Sci**, 45:1109-1116, 2004.
6. P. Bezwada, L. Clark, S.Adams, T. O'Brien, G.Schultz. Comparative Ocular Bioavailability and Efficacy of Topical Levofloxacin and Ofloxacin in Rabbits, **J Toxicol Cutaneous Ocular Toxicol**, 23:83-90, 2004.
7. L. Clark, P. Bezwada, K. Hosoi, T. Ikuse, S. Adams, G. Schultz, T. O'Brien. Comprehensive Evaluation of Ocular Toxicity of Levofloxacin in Rabbit and Primate Models. **J Toxicol Cutaneous Ocular Toxicol**, 23:1-18, 2004.
8. D.W. Esson, A. Neelakantan, A.A. Iyer, T.D. Blalock, L. Balasubramanian, G.R. Grotendorst, G.S. Schultz, M.B. Sherwood. Expression of Connective Tissue Growth Factor After Glaucoma Filtration Surgery in a Rabbit Model. **Invest Ophthalmol Vis Sci**, 45:485-491, 2004.
9. F.J. Ollivier, D.E. Brooks, G.S. Schultz, T.D. Blalock, S.E. Andrew, A.M. Komaromy, T.J. Cutler, M.E. Lassaline, M.E. Kallberg, G.B. van Setten. Connective Tissue Growth Factor in Tear Film of the Horse: Detection, Identification and Origin. **Graefe's Archiv Clin Exp Ophthalmol**, 242:165-171, 2004.
10. F.J. Ollivier, D.E. Brooks, M.E. Kallberg, A.M. Komaromy, M.E. Lassaline, S.E. Andrew, K.N. Gelatt, G.R. Stevens, T.D. Blalock, G.B. van Setten, G.S. Schultz. Inhibition of Matrix Metalloproteinase Activities in the Tear Film of Horses With Ulcerative Keratitis, **Am J Vet Res**, 64:1081-1087, 2003.
11. J.G. Wilmoth, P.J. Antonelli, G.S. Schultz. Tympanic Membrane Metalloproteinases Inflammatory Response. **Otolaryngol Head Neck Surg**, 129:647-654, 2003.
12. S.O. Canapp Jr., J.P. Farese, G.S. Schultz, S. Gowda, A.M. Ishak, S.F. Swaim, J. VanGilder, L. Lee-Ambrose, F.G. Martin. The Effect of Topical Tripeptide-Copper-Complex on Healing of Ischemic Open Wounds. **Vet Surgery**, 32:515-523, 2003.
13. K.C. Flanders, C.D. Major, A. Arabshahi, E.D. Aburime, K.H. Okada, K. Fujii, T.D. Blalock, G.S. Schultz, A. Sowers, M.A. Anzano, J.B. Mitchell. A. Russo, A.B. Roberts. Interference with TGFb/SMAD3 Signaling Results in Accelerated Healing of Wounds in Previously Irradiated Skin. **Am J Pathol**, 163:2247-2257, 2003.
14. G.A. Chin, T.G. Thigpin, K.J. Perrin, L.L. Moldawer, G.S. Schultz. Treatment of Chronic Ulcers in Diabetic Patients with a Topical Metalloproteinase Inhibitor, Doxycycline, **Wounds**, 15:315-323, 2003.
15. J.T. Daniels, G.S. Schultz, T.D. Blalock, Q. Garrett, G.R. Grotendorst, N.M. Dean, P.T. Khaw. Mediation of TGFβ1-Stimulated Contraction of Matrix Contraction by Fibroblasts: A Role for CTGF in Contractile Scarring. **Am J Pathol**, 163:2043-2052, 2003.
16. H.N. Paddock, G.S. Schultz, H.V. Baker, J.C. Varela, E.A. Beierle, L.L. Moldawer, D.W. Mozingo. Analysis of Gene Expression Patterns in Human Post-Burn Hypertrophic Scars. **J Burn Care Rehap** 24:371-377, 2003.
17. J.G. Wilmoth, P.J. Antonelli, G.S. Schultz. Matrix Metalloproteinases in a Gerbil Cholesteatoma Model. **Otolaryngol Head Neck Surg**, 129:402-407, 2003.
18. P.J. Antonelli, G.S. Schultz, D.J. Sundin, P.A. Pemberton, P.J. Barr. Protease Inhibitors Alpha-1 Antitrypsin and Ilomastat Are Not Ototoxic in the Chinchilla. **Laryngoscope**, 113:1764-1769, 2003.
19. P. Antonelli, G. S. Schultz, K.M. Kim, J.S. Cantwell, D.J. Sundin, P.A. Pemberton, P.J. Barr. Alpha 1-Antitrypsin and Ilomastat Inhibit Inflammatory Proteases Present In Human Middle Ear Effusions, **Laryngoscope**, 113:1347-1351, 2003.
20. G.B. van Setten, M. Aspiotis, T.D. Blalock, G. Grotendorst, G.S. Schultz. Connective Tissue Growth Factor in Pterygium: Simultaneous Presence with Vascular Endothelial Cell Growth Factor – Possible Contributing Factor to Conjunctival Scarring. **Graefe's Arch Clin Exp Ophthalmol** 241:135-139, 2003.
21. R. Lobmann, G Schultz, H. Lehnert. Molekulare Grundlagen der Wundheilung bei diabetishchen Fußsytndrom. **Medizinische Klinik** 98:292-301, 2003.

22. J.T. Daniels, A.D. Cambrey, N.L. Occleston, Q. Garrett, R.W. Tarnuzzer, G.S. Schultz, and P.T. Khaw. Matrix Metalloproteinase Inhibition Modulates Fibroblast-Mediated Matrix Contraction and Production *In Vitro.* **Invest Ophthalmol Vis Sci** 44:1104-1110, 2003.
23. M.K. Mazaheri, G.S. Schultz, T.D. Blalock, H.H. Caffee, G.A. Chin. Role of Connective Tissue Growth Factor in Breast Implant Elastomer Capsular Formation. **Ann Plastic Surg** 50:1-6, 2003.
24. M.F. Cordeiro A. Mead, R.R. Ali, R.A. Alexander, S. Murray, C. Chen, C. York-Defalco, N.M. Dean, G.S. Schultz, P.T. Khaw. Novel Antisense Oligonucleotides Targeting TGF-Beta Inhibit *In Vivo* Scarring And Improve Surgical Outcome. **Gene Therapy** 10:59-71, 2003.
25. G.B. van Setten, T.D. Blalock, G. Grotendorst, G.S. Schultz. Detection of Connective Tissue Growth Factor (CTGF) in Human Tear Fluid: Preliminary Results. **Acta Ophthalmologica Scand**, 81:51-53, 2003.
26. T.D. Blalock, M.R. Duncan, J.C. Varela, M.H. Goldstein, S. Tuli, G. Grotendorst, and G.S. Schultz. Connective Tissue Growth Factor Expression and Action in Human Corneal Fibroblasts Cultures and Rat Corneas Following Photorefractive Keratectomy. **Invest Ophthalmol Vis Sci** 44:1879-1887, 2003.
27. R.R. Mohan, G.S. Schultz, J.W. Hong, R.R. Mohan, S.E. Wilson. Gene Transfer Into Rabbit Keratocytes Using AAV and Lipid-Mediated Plasmid Vectors With a Lamellar Flap for Stromal Access. **Exp Eye Res** 76:373-383, 2003.
28. G.B. van Setten, T.D. Blalock, G.R. Grotendorst, G.S. Schultz, Detection of Connective Tissue Growth Factor in Human Aqueous Humor. **Ophthalmic Res**, 34:306-308, 2002.
29. R.G. Crystal, P.B. Bitterman, B. Mossman, M.I. Schwartz, L. Almasy, H.A. Chapman, S.L. Friedman, T.E. King, Jr., L.A. Leinwand, L. Liotta, G.R. Martin, D.A. Schwartz, G.S. Schultz, C.R. Wagner, and R.A. Musson. Future Research Directions in Idiopathic Pulmonary Fibrosis: A Summary of a National Heart, Lung, and Blood Institute Working Group. **Am J Resp Crit Care Med**, 166:23-246, 2002.
30. R. Lobmann, A. Ambrosch, G. Schultz, K. Waldmann, S. Schieweck, H. Lehnert. Expression of Matrix-Metalloproteinases and Their Inhibitors in the Wounds of Diabetic and Non-Diabetic Patients. **Diabetologia** 45:1011-1016, 2002.
31. J.C. Varela, M.H. Goldstein, H.V. Baker, G.S. Schultz. Microarray Analysis of Gene Expression Patterns During Healing of Rat Corneas After Excimer Laser Photorefractive Surgery. **Invest Ophthalmol Vis Sci** 1772-1782, 2002.
32. G.P. Ladwig, M.C. Robson, R. Liu, M.A. Kuhn, D.F. Muir, G.S. Schultz. Ratios of Activated MMP-9/TIMP-1 in Wound Fluids Are Inversely Correlated With Healing of Pressure Ulcers. **Wound Rep Reg** 26-37, 2002.
33. D.H. Lehman, P.J. Antonelli, J.G. Wilmoth, A.R. Prevatt, G.S. Schultz. Inhibition of Matrix Metalloproteinases in Gerbil Cholesteatoma. **Otolaryngol Head Neck Surg** 126:404-408, 2002.
34. A.J. Cowin, N. Hatzirodos, C.A. Holding, V. Dunaiski, R.H. Harries, T.E. Rayner, R. Fitridge, R.D. Cooter, G.S. Schultz and D.A. Belford. Effect of Healing on the Expression of Transforming Growth Factor-∃s and Their Receptors in Chronic Venous Leg Ulcers. **J Invest Dermatol** 117:1282-1289, 2001.
35. G.L. Locksmith, P. Clark, P. Duff, G.R. Saade, G.S. Schultz. Amniotic Fluid Concentrations of Matrix Metalloproteinase 9 and Tissue Inhibitor of Metalloproteinase 1 During Pregnancy and Labor. **Am J Obstet Gynecol** 184:159-164, 2001.
36. N. Dushku, M.K. John, G.S. Schultz, T.W. Reid. Pterygia Pathogenesis: Corneal Invasion by Matrix Metalloproteinase Expressing Altered Limbal Epithelial Basal Cells and Activation of Fibroblasts. **Arch Ophthalmol** 119:695-706, 2001.
37. D.T. Strubbe, D.E. Brooks, G.S. Schultz, H. Willis-Goulet, K.N. Gelatt, S.E. Andrew, M.E. Kallberg, E.O. Mackay, W.R. Collante. Evaluation of Tear Film Proteinases in Horses with Ulcerative Keratitis. **Vet Ophthalmol** 3:111-119, 2000
38. C. Chen, B. Michelini-Norris, S. Stevens, J. Rowsey, X. Ren, M. Goldstein, and G.S. Schultz. Quantitative Measurement of mRNAs for Transforming Growth Factor-∃ and Extracellular Matrix Proteins in Rat Corneas After Excimer Laser Keratectomy. **Invest Ophthalmol Vis Sci** 41:4108-4116, 2000.
39. G.J. Angella, M.B. Sherwood, L. Balasubramanian, W. Doyle, M.F. Smith, G. van Setten, M. Goldstein, G.S. Schultz. Collagen Shield Enhances Plasmid Transfection of Filtration Surgery Tissues. **Invest Ophthalmol Vis Sci** 41: 4158-4162, 2000.
40. V.C. Mudera, R. Pleass, M. Eastwood, R. Tarnuzzer, G. Schultz, P. Khaw, D.A. McGrouther, R.A. Brown. Molecular Responses of Human Dermal Fibroblasts to Dual Cues: Contact Guidance and Mechanical Load. **Cell Motility Cytoskeleton** 45:1-9, 2000.
41. M.F. Cordeiro, S.S. Bhattacharya, G.S. Schultz, P.T. Khaw. TGF-ß1, -ß2 & -ß3 *In Vitro*: Biphasic Effects on Tenon's Fibroblast Contraction, Proliferation & Migration. **Invest Ophthalmol Vis Sci** 41:756-763, 2000.
42. Y.T. Konttinen, P. Kemppinen, T.F. Li, H. Pihlajam≅ki, T. Sorsa, M. Takagi, S. Santavirta, G.S. Schultz, M.G. Humphreys-Beher. Transforming and Epidermal Growth Factors in Degenerated Intervertebrate Discs. **J Bone Joint Surg** 81:1058-1063, 1999.
43. C. Chen, G.S. Schultz, M. Bloch, P.D. Edwards, S. Tebes, D. Mills, B.A. Mast. Molecular and Mechanistic Validation of Delayed Healing Rat Wounds as a Model for Human Chronic Wounds. **Wound Rep Regen** 7:486-

494, 1999.

44. G.J. Locksmith, P. Clark, P. Duff, G.S. Schultz. Amniotic Fluid Matrix Metalloproteinase-9 Levels in Women with Preterm Labor and Suspected Intra-amniotic Infection. **Obstet Gynecol** 94:1-6, 1999.
45. M. John, G. Schultz, T.N. Rajaleksbmi, M.B. Nair. Immunolocalization and Quantitation of Transforming Growth Factor alpha in Hydatidiform Moles. **Tumori,** 85:179-183, 1999.
46. B.K. Pilcher, J. Dunin, B.A. Mast, G.S. Schultz, W.C. Parks, H.G. Welgus. Keratinocyte Collagenase-1 Expression Requires an Epidermal Growth Factor Receptor Autocrine Mechanism. **J Bio Chem** 274:10372-10381, 1999.
47. G.B. van Setten, L. Edström, H. Stibler, S. Rasmussen, and G. Schultz. Levels of Transforming Growth Alpha (TGF-∀) in Human Cerebrospinal Fluid. **Int J Dev Neuroscience** 17:131-134, 1999.
48. S. Tomas-Barberan, G.S. Schultz, R.W. Tarnuzzer, P. Fagerholm. Messenger RNA Levels of Genes Involved in Extracellular Matrix From Human Corneal Scrapings Before and After Photorefractive Keratectomy. **Acta Ophthalmol Scandinavia** 76:568-572, 1998.
49. M.B. Witte, F.J. Thornton, T. Kiyama, D.T. Efron, G.S. Schultz, L.L. Moldawer, and A. Barbul. Metalloproteinase Inhibitors and Wound Healing: A Novel Enhancer of Wound Strength. **Surgery** 124:464-470, 1998.
50. A. Avidano, C.S. Cotter, S.P. Stringer, G.S. Schultz. Analysis of Protease Activity in Human Otitis Media. **Otolaryngology Head Neck Surg** 119:346-351, 1998.
51. N.J. Trengove, M.C. Stacey, S. Macauley, N. Bennett, J. Gibson, F. Burslem, G. Murphy, and G. Schultz. Analysis of Acute and Chronic Wound Environments: The Role of Proteases and their Inhibitors. **Wound Rep Reg** 7:442-452, 1997.
52. Dou, R.W. Tarnuzzer, R.S. Williams, G.S. Schultz, and N. Chegini. Differential Expression of Matrix Metalloproteinase and Their Tissue Inhibitors in Leiomyomata: A Mechanism for Gonadotropin Releasing Hormone Agonist-Induced Tumor Regression. **Molecular Human Reprod** 3:1005-1014, 1997.
53. J.W. Doyle, M.F. Smith, J.T. Garcia, G. Schultz and M.B. Sherwood. Treatment of Bleb Leaks with Transforming Growth Factor-∃ in the Rabbit Model. **Invest Ophthalmol Vis Sci** 38:1630-1634, 1997.
54. C.C. Solorzano, R. Ksontini, J.H. Pruitt, T. Auffenberg, C. Tannahill, R.E. Galardy, G.S. Schultz, S.L.D. MacKay, E.M. Copeland, III, and L.L. Moldawer. A Matrix Metalloproteinase Inhibitor Prevents Processing of Tumor Necrosis Factor Alpha (TNF∀) and Abrogates Endotoxin-Induced Lethality. **Shock** 7:427-431, 1997.
55. P. Balarm, M. John, T.N. Rajalekshmy, B. Nair, G. Schultz, and K. Nair. Expression of Epidermal Growth Factor in Gestational Trophoblastic Diseases. **J Cancer Res Clin Oncol,** 123: 161-166,1997.
56. M. John, T.N. Rajalekshmy, B. Nair, J. Augustine, G. Schultz, K.M. Nair, and P. Balarm. Expression of Epidermal Growth Factor and its Receptor in Gestational Trophoblastic Diseases. **Oncology Reports** 4:177-182,1997.
57. N.L. Occleston, J.T. Daniels, R.W. Tarnuzzer, K.K. Sethi, R.A. Alexander, S.S. Bhattacharaya, G.S. Schultz, and P.T. Khaw. Single Exposure to Antiproliferatives: Long-Term Effects on Ocular Fibroblast Wound Healing Behavior. **Invest Ophthalmol Vis Sci** 38:1998-2007, 1997.
58. G.S. Ashcroft, M.A. Horan, R.W. Tarnuzzer, G.S. Schultz, M.A. Horan, and M.W.J. Ferguson. Estrogen Accelerates Cutaneous Wound Healing Associated with an Increase in TGF-∃1 Levels. **Nature Medicine** 3:1209-1215, 1997.
59. G.S. Ashcroft, S.E. Herrick, R.W. Tarnuzzer, G.S. Schultz, M.A. Horan, and M.W.J. Ferguson. Age-Related Changes in the Temporal and Spatial Regulation of Matrix Metalloproteinases (MMP) Protein and mRNA Profiles in Normal Skin and Acute Cutaneous Wounds of Healthy Humans. **Cell Tissue Res** 290:581-591, 1997.
60. G.S. Ashcroft, S.E. Herrick, R.W. Tarnuzzer, M.A. Horan, G. Schultz, and M.W.J. Ferguson. Human Ageing Impairs Injury-Induced *in Vivo* Expression of Tissue Inhibitors of Matrix Metalloproteinases (TIMP)-1 and -2 Proteins and mRNA. **J Pathol** 183:169-176, 1997.
61. C.C. Solórzano, S.C. Jones, M. Pettijean, T.G. O'Daniel, T. Auffenberg, P.G. Woost, E.M. Copeland, III, G.S. Schultz, and S.L.D. MacKay. Inhibition of Transforming Growth Factor Alpha Stimulation of Human Squamous Cell Carcinoma of the Head and Neck with Anti-TGF-∀ Antibodies and Tyrphostin. **Ann Surg Oncol** 4:670-684,1997.
62. L.E. Franzen, M.R. Ghassenifar, B. Lonnberg, G.S. Schultz. Stimulation Of Protracted Connective Tissue Repair In Normal Mice By Transforming Growth Factor ∃1. **Scand J Plast Reconstr Hand Surg** 30:267-273, 1996.
63. M.R. Ghassemifar, R.W. Tarnuzzer, N. Chegini, E. Tarila, G.S. Schultz, and L.E. Franzen. Expression of Alpha-Smooth Muscle Actin, TGF-∃1, and TGF-∃ Type II Receptor mRNA During Connective Tissue Contraction. **In Vitro Cell Dev Biol** 33:622-627, 1997.
64. S.P. Macauley, R.W. Tarnuzzer, G.S. Schultz, N. Chegini, G.E. Oxford, and M.G. Humphreys-Beher. Extracellular-Matrix Gene Expression During Mouse Submandibular Gland Development. **Arch Oral Biol** 42:443-454, 1997.

65. Q. Dou, Y. Zhao, R.W. Tarnuzzer, H. Rong, R.S. Williams, G.S. Schultz, and N. Chegini. Suppression of Transforming Growth Factor-Beta (TGF-∃) and TGF-∃ Receptor Messenger Ribonucleic Acid and Protein Expression in Leiomyomata in Women Receiving Gonadotropin-Releasing Hormone Agonist Therapy. **J Clin Endocrinol Metab** 81:3222-3230, 1996.
66. S.P. Macauley, G.S. Schultz, B.A. Buckner, J.L. Laz, S.A. Krawetz, and T.P. Yang. Effects of Transforming Growth Factor Alpha on Extracellular Matrix Gene Expression by Human Fibroblasts From a Laryngeal Stenotic Lesion. **Wound Repair Regen** 4:269-277, 1996.
67. C.S. Cotter, M.A. Avidano, S.P. Stringer, and G.S. Schultz. Experimental Inhibition of Proteases in Pseudomonas Otitis Media in Chinchillas. **Otolaryngol Head Neck Surgery** 115:342-251, 1996.
68. R.W. Tarnuzzer, S.P. Macauley, W.G. Farmerie, S. Cabellaro, M.R. Ghassemifar, J.T. Anderson, C.R. Robinson, M.B. Grant, M.G. Humphreys-Beher, L. Franzen, A.B. Peck, and G.S. Schultz. Competitive RNA Templates for Detection and Quantification of Growth Factors, Cytokines, Extracellular Matrix Components, and Matrix Metalloproteinases by RT-PCR. **Biotechniques** 20:670-674, 1996.
69. J.P. Barletta, G.J. Angella, K.C. Balch, H.G. Dimova, G.A. Stern, M.T. Moser, G.B. van Setten and G.S. Schultz. Inhibition of Pseudomonal Ulceration in Rabbit Corneas by a Synthetic Matrix Metalloproteinase Inhibitor. **Invest Ophthalmol Vis Sci** 37:20-28, 1996.
70. G.B. van Setten, S.P. Macauley, M. Humphreys-Beher, N. Chegini and G. Schultz. Detection of Transforming Growth Factor-∀ mRNA and Protein in Rat Lacrimal Glands and Characterization of Transforming Growth Factor-∀ in Human Tears. **Invest Ophthalmol Vis Sci** 37:166-173, 1996.
71. A.V. Nall, R.E. Brownlee, C.P. Colvin, G.S. Schultz, D. Fein, T Lui, A. Kalra, N.J. Cassisi. Transforming Growth Factor Beta-1 Improves Wound Healing and Random Flap Survival in Normal and Irradiated Rats. **Arch Otolaryngol Head Neck Surg** 122:171-177, 1996.
72. G.B. van Setten, P. Fagerholm, B. Philipson, G. Schultz. Growth Factors and Their Receptors in the Anterior Chamber – Absence of Epidermal Growth Factor and Transforming Growth Factor Alpha in Human Aqueous Humor. **Ophthalmic Res** 28:361-364, 1996.
73. Nilsson, B. Wangberg, L. Kolby, G.S. Schultz, and H. Ahlman. Expression of Transforming Growth Factor alpha and Its Receptor in Human Neuroendocrine Tumors. **Int J Cancer** 60:645-651, 1995.
74. K.R. Purushotham, K. Offenmüller, A.T. Bui, T. Zelles, J. Blazsek, G.S. Schultz, and M.G. Humphreys-Beher. Absorption of Epidermal Growth Factor Occurs Through the Gastrointestinal Tract and Oral Cavity in the Adult Rat. **A J Physiol** 269:G867-G873, 1995.
75. S.L.D. MacKay, L.R. Yaswen, R.T. Tarnuzzer, L.L. Moldawer, K.I. Bland, E.M. Copeland and G.S. Schultz. Colon Cancer Cells That Are Not Growth Inhibited by TGF-∃ Lack Functional Type I and II TGF-∃ Receptors. **Ann Surg** 221:767-777, 1995.
76. G.B. van Setten and G.S. Schultz. Transforming Growth Factor Alpha is a Constant Component of Human Tear Fluid. **Graefe's Archiv Clin Exp Ophthalmol** 232:523-526, 1994.
77. S.E. Wilson, Y-G. He, J. Weng, J.D. Zeiske, J.V. Jester, and G.S. Schultz. Effect of Epidermal Growth Factor, Hepatocyte Growth Factor, and Keratinocyte Growth Factor on Proliferation, Motility and Differentiation of Human Corneal Epithelial Cells. **Exp Eye Res** 59:665-678, 1994.
78. P. Malcherek, G. Schultz, U. Wingren, and L. Franzen. Formation of Healing Tissue and Angiogenesis in Repair of Connective Tissue Stimulated by Epidermal Growth Factor. **Scan J Plast Reconstr Hand Surg** 28:1-7, 1994.
79. S.E. Wilson, G.S. Schultz, N. Chegini, J. Weng, and Y.G. He. Epidermal Growth Factor, Transforming Growth Factor Alpha, Transforming Growth Factor Beta, Acidic Fibroblast Growth Factor, Basic Fibroblast Growth Factor, and Interleukin-1 Proteins in the Cornea. **Exp Eye Res** 59:63-72, 1994.
80. M.G. Humphreys-Beher, S.P. Macauley, N. Chegini, G.B. van Setten, K. Purushotham, C. Stewart, T.T. Wheeler, and G.S. Schultz. Characterization of the Synthesis and Secretion of TGF-∀ from Salivary Glands and Saliva. **Endocrinology** 134:963-970, 1994.
81. D.S. Rotatori, N.C. Kerr, B. Raphael, B.J. McLaughlin, G.A. Stern, and G.S. Schultz. Transforming Growth Factor Alpha in Cat Anterior Chamber Fluid After Endothelial Injury. **Invest Ophthalmol Vis Sci** 35:143-149, 1994.
82. P. Malcherek, G. Schultz, U. Wingren, and L. Franzen. Effect of Epidermal Growth Factor on Cell Proliferation in Normal and Wounded Connective Tissue. **Wound Rep Reg** 1:63-68, 1993.
83. J.D. King, S.P. Stringer, N. Chegini, W.H. Donnelly, N.J. Cassisi, and G.S. Schultz. Transforming Growth Factor Alpha Protein and Receptor Localization in Normal and Healing Laryngotracheal Tissue. **Otolaryngol Head Neck Surg** 109:915-925, 1993.
84. B. Raphael, N.C. Kerr, R.W. Shimizu, J.H. Lass, K.C. Crouthamel, S.R. Glaser, G.S. Schultz, B.J. McLaughlin, and D.C. Musch. Enhanced Healing of Cat Corneal Endothelial Wounds by Epidermal Growth Factor. **Invest Ophthalmol Vis Sci** 34:2305-2312, 1993.
85. R.M. Salloum, G.S. Schultz, and W.W. Souba. Regulation of Small Intestinal Substrate Transport by Epidermal Growth Factor. **Surgery** 113:552-559, 1993.

86. L. Franzen, R. Ghassenifar, and G. Schultz. Specific Binding of EGF in Connective Tissue Repair. **Euro J Cell Biol** 60:346-350, 1993.
87. P.T. Khaw, J.W. Doyle, M.B. Sherwood, I. Grierson, S. McGorray, and G. Schultz. Prolonged Localized Tissue Effects from 5-Minute Exposures to 5-Fluorouracil and Mitomycin-c. **Arch Ophthalmol 111**:263-267, 1993.
88. N. Chegini, M.J. Rossi, G.S. Schultz, W.A. Dunn, Jr., and B.J. Masterson. Cellular Distribution of EGF, TGF-∀ and EGF Receptor in Fascia Peritoneum During Healing: an Autoradiographic and Immunohistochemical Study. **Wound Rep Reg** 1:28-40, 1993.
89. P.T. Khaw, M.B. Sherwood, J.W. Doyle, M.F. Smith, I. Grierson, S. McGorray, and G.S. Schultz. Intraoperative and Postoperative Treatment with 5-Fluorouracil and Mitomycin-c: Long Term Effects *In Vivo* on Subconjunctival and Scleral Fibroblasts. **Internatl Ophthalmol** 16:381-385, 1992.
90. G.S. Schultz, S. Strelow, G.S. Stern, N. Chegini, M.B. Grant, R.E. Galardy, D. Grabelny, J.J. Rowsey, C. Stonecipher, and V. Parmley. Inhibition of Cornea Ulceration After Severe Alkali Injury by a Synthetic Metalloproteinase Inhibitor. **Invest Ophthalmol Vis Sci** 33:3325-3331, 1992.
91. M.B. Grant, P.T. Khaw, G.S. Schultz, J.L. Adams, and R.W. Shimizu. Effects of Epidermal Growth Factor, Fibroblast Growth Factor and Transforming Growth Factor Beta on Corneal Cell Chemotaxis. **Invest Ophthalmol Vis Sci** 33:3292-3301, 1992.
92. P.T. Khaw, S.L.D. MacKay, N. Chegini, and G.S. Schultz. Detection of Transforming Growth Factor-∀ Messenger RNA and Protein in Human Corneal Epithelial Cells. **Invest Ophthalmol Vis Sci** 33:3302-3306, 1992.
93. J.S. Sanfilippo, Ch.V. Rao, J.J. Guarnaschelli, P.G. Woost, V.M. Byrd, E. Jones and G.S. Schultz. Detection of Epidermal Growth Factor and Transforming Growth Factor Alpha Protein in Meningiomas and Other Tumors of the Central Nervous System in Human Beings. **Surg Gynecol Obstet** 177:488-496, 1993.
94. P.T. Khaw, M.B. Sherwood, S.L.D. MacKay, M.J. Rossi, and G. Schultz. Five-Minute Treatments with Fluorouracil, Fluorouridine and Mitomycin Have Long-term Effects on Human Tenon's Fibroblasts. **Arch Ophthalmol** 110:1150-1154, 1992.
95. F. Bissionnette, C. Cook, T. Geoghegan, M. Steffan, J. Henry, M.A. Yussman, and G. Schultz. Transforming Growth Alpha and Epidermal Growth Factor mRNA and Protein Levels in Early Mid and Late Gestation Human Placenta. **Am J Obstet Gynecol** 166:192-199, 1992.
96. U. Wingren, L. Franzen, G.M. Larson, P. Malcherak, and G.S. Schultz. Epidermal Growth Factor Accelerates Connective Tissue Wound Healing in the Perforated Rat Mesentery. **J Surg Res** 52:48-54, 1992.
97. S.C. Jones, L.J. Curtsinger, J.D. Whalen, J.D. Pietsch, D. Ackerman, G.L. Brown and G.S. Schultz. Effect of Topical Recombinant TGF-∀ on Healing of Partial Thickness Injuries. **J Surg Res** 51:344-352, 1991.
98. R.S. Williams, G.S. Schultz, N. Chegini, and A.M. Rossi. Effect of Transforming Growth Factor Beta on Post Operative Adhesions Formation and Intact Peritoneum. **J Surg Res** 52:65-70, 1992.
99. G.S. Schultz, L. Cipollo, A. Whitehouse, R.A. Eiferman, P. Woost and M. Jumblatt. Growth Factors and Corneal Endothelial Cells: III. Stimulation of Adult Human Corneal Endothelial Cell Mitosis in Vitro by Defined Mitogenic Agents. **Cornea** 11:20-27, 1992.
100. P.G. Woost, M.M. Jumblatt, R.A. Eiferman and G.S. Schultz. Growth Factors and Corneal Endothelial Cells: II. Characterization of Epidermal Growth Factor Receptor from Bovine Corneal Endothelial Cells. **Cornea** 11:11-19, 1992.
101. P.G. Woost, M. M. Jumblatt, R.A. Eiferman and G.S. Schultz. Growth Factors and Corneal Endothelial Cells: I. Stimulation of Bovine Corneal Endothelial Cell DNA Synthesis in Defined Growth Factor. **Cornea** 11:1-10, 1992.
102. G.L. Brown, L.J. Curtsinger, M.J. Jurkiewicz, and G.S. Schultz. Stimulation of Healing of Chronic Wounds by Epidermal Growth Factor. **Plastic Reconstr Surgery** 88:189-196, 1991.
103. T.G. O'Daniel, M. Petitjean, J. Zogg, J.K. Lasseter, S.A. Martinez, M.B. Nolph and G.S. Schultz. Characterization of Epidermal Growth Factor Binding and Action on Tympanic Membranes. **Ann Otol Rhinol Laryngol** 99:80-84, 1990.
104. D.S. Rotatori, H.H. Caffee, E.M. Copeland, and G.S. Schultz. Growth Factors are Present in Human Wound Fluid. **Surgical Forum** 41: 627-630, 1990.
105. J.S. Thompson, S.K. Saxena, C. Greaton, G. Schultz and J.G. Sharp. The Effect of the Route of Delivery of Urogastrone on Intestinal Regeneration. **Surgery** 106:45-51, 1989.
106. J.B. Fassio, E.B. Brockman, M. Jumblatt, C. Creaton, J.I. Henry, T.E. Georghegan, C.C. Barr, and G.S. Schultz. Transforming Growth Factor Alpha and Its Receptor In Neural Retina. **Invest Ophtholomol Vis Sci** 30:1916-1922, 1989.
107. G.L. Brown, L.B. Nanney, J. Griffen, A.B. Cramer, J.M. Yancey, L.J. Curtsinger, L. Holtzin, G.S. Schultz, M.J. Jurkiewicz and J.B. Lyncy. Enhancement of Wound Healing by Topical Treatment With Epidermal Growth Factor. **New Eng J Med** 321:76-79, 1989.
108. M.J. Brown, J.L. Zogg, G.S. Schultz and F.K. Hilton. Increased Binding of Epidermal Growth Factor at Implantation Sites in Mouse Uteri. **Endocrinology** 124:2882-2888, 1989.

109. L.J. Curtsinger, J.D. Pietsch, G.L. Brown, A. von Fraunhofer, D. Ackerman, H.C. Polk, Jr., and G.S. Schultz. Reversal of Adriamycin-Impaired Wound Healing by TGF-∃. **Surgery Gyn Obstet** 168:517-522,1989.
110. S.C. Jones, G.S. Schultz, and S.A. Martinez. Characterization of Transforming Growth Factor-∀ Binding and Action on Squamous Cell Carcinoma Cells. **Surgical Forum** 40: 533-535, 1989
111. G.S. Schultz, G.L. Brown, L.J. Curtsinger, M. White, R.O. Mitchell, J. Pietsch, R. Nordquist and A. von Fraunhofer. Acceleration of Tensile Strength of Incisions Treated with EGF and TGF-∀ . **Ann Surg** 208:788-794, 1988.
112. G.E. Hofmann, C.V. Rao, M.J. Brown, L.F. Murray, G.S. Schultz and T.A. Siddigi. Human Epidermal Growth Factor Concentrations in Urine of Nonpregnant and Pregnant Women Throughout Pregnancy and at Delivery. **J Clin Endocrinol Metab** 66:119-123, 1988.
113. K. Darlak, G. Franklin, P. Woost, E. Sonnenfeld, D. Twardzik, A. Spatola and G.S. Schultz. Assessment of Biological Activity of Synthetic Fragments of Transforming Growth Factor-∀. **J Cell Biochem** 36:341-352, 1988.
114. S.C. Jones, C.J. Greaton, M. Pettijean, S.A. Martinez and G.S. Schultz. Regulation of Squamous Cell Carcinoma Cell Growth By Transforming Growth Factor-∀ and Epidermal Growth Factor. **Surgical Forum** 39: 548-550, 1988.
115. U. Wingren, G.M. Larson, C.J. Greaton, and G.S. Schultz. Intravenous But Not Intragastric Epidermal Growth Factor Inhibits Acid Secretion. **Surgical Forum** 39: 75-77, 1988.
116. L.J. Curtsinger, J.D. Pietsch, G.S. Schultz, G.L. Brown, and H.C. Polk. Reversal of Adriamycin-Impaired Wound Healing By Transforming Growth Factor Beta. **Surgical Forum** 38: 608-610, 1988
117. I.H. Silverman, C.L. Cook, J.S. Sanfilippo, M.A. Yussman, G.S. Schultz and F.K. Hilton. Ham's F-10 Constituted with Tap Water Supports Mouse Conceptus Development In Vitro. **J In Vitro Fert** 4:185-187, 1987.
118. G.S. Schultz, M. White, G. Brown, J. Lynch, D.R. Twardzik and G. J. Todaro. Epithelial Wound Healing Enhanced by Transforming Growth Factor-∀ and Vaccinia Growth Factor. **Science** 235:350-352 1986.
119. N.A. Muma, P.R. Rowell and G.S. Schultz. Effects of Long-Term Dietary Choline and Phosphatidylcholine Administration on Muscarinic Receptors in Aged Mouse Brain. **Neurolog Res** 10:130-135, 1988.
120. M.J. Brown, C.L. Cook, J.L. Henry and G.S. Schultz. Levels of Epidermal Growth Factor Binding in Third Trimester and Term Human Placenta: Elevated Binding in Term Placentas of Male Fetuses. **Am J Obstet Gynecol** 156:716-720, 1987.
121. M. Petitjean, C.J. Greaton, S.A. Martinez, T.E. Geoghegan and G.S. Schultz. Production of Transforming Growth Factor-∀ in Head and Neck Carcinomas. **Surgical Forum** 38: 574-576, 1987.
122. N. Ramani, N. Chegini, C.V. Rao, P. Woost and G.S. Schultz. The Presence of Epidermal Growth Factor Binding Sites in the Intracellular Organelles of Term Placenta. **J Cell Sci** 84:19-40, 1986.
123. F. DeLeon, R. Vijayakumar, M. Brown, C.V. Rao, M.A. Yussman and G.S. Schultz. Peritoneal Fluid Estrogen, Progesterone, PGF_2 , PGE_2, and Epidermal Growth Factor in Patients With or Without Endometriosis. **Obstet Gynecol** 62:189-194 1986.
124. G. Brown, J. Brightwell, L. Curtsinger, H. Polk, J. Merryweather, P. Valenzuela and G. Schultz. Enhancement of Epidermal Regeneration by Biosynthetic Epidermal Growth Factor. **J Exp Med** 163:1319-1324, 1986.
125. T. O'Daniel, S. Martinez, G. Schultz, J. Lassetter, P. Woost, S. Jones, and K. Walker. Epidermal Growth Factor Receptors in Head and Neck Tumors. **Surgical Forum** 37: 568-570, 1986.
126. C.V. Rao, N. Ramani, N. Chegini, F. Carman, B. Stadig, P. Woost, G. Schultz and C. Cook. Topography of Human Placental Binding Sites for Epidermal Growth Factor. **J Biol Chem** 260:1705-1710, 1985.
127. P.G. Woost, J. Brightwell, R.A. Eiferman and G.S. Schultz. Effect of Growth Factors with Dexamethasone on Corneal Stromal Wound Healing. **Exp Eye Res** 40:47-60, 1985.
128. J. Brightwell, R.A. Eiferman, P. Valenzuela, P.J. Barr, J.P. Merryweather and G.S. Schultz. Acceleration of Corneal Wound Healing in Primates by Human Epidermal Growth Factor. **Invest Ophthalmol Vis Sci** 26:105-110, 1985.
129. L.J. Curtsinger, III, G.S. Schultz and G.L. Brown. Progress in Burn Therapy: Skin Banking and Epidermal Culture. **J. Kentucky Med. Assoc.** pp. 251-253, 1985.
130. M.J. Brown, G.S. Schultz and F.K. Hilton. Intrauterine Proximity to Male Fetuses Predetermines Level of Epidermal Growth Factor in Submandibular Glands of Adult Female Mice. **Endocrinology** 115:2318-2323, 1984.
131. C.V. Rao, F.R. Carman, N. Chegini and G.S. Schultz. Binding Sites for Epidermal Growth Factor in Human Fetal Membranes. **J Clin Endocrinol Metab** 58:1034-1042, 1984.
132. S.L. Fitzpatrick, J. Brightwell, J.L. Wittliff, G.H. Barrows and G.S. Schultz. Epidermal Growth Factor Receptors in Breast Tumor Biopsies: Relationship to Estrogen Receptor Levels. **Cancer Res** 44:3448-3453, 1984.
133. S.L. Fitzpatrick, M.P. LaChance and G.S. Schultz. Characterization of Epidermal Growth Factor Receptor and Action on Human Breast Cancer Cells in Culture. **Cancer Res** 44:3442-3447, 1984.
134. G.E. Hofmann, C.V. Rao, G.H. Barrows, G.S. Schultz and J.S. Sanfilippo. Binding Sites for Epidermal Growth Factor in Human Uterine Tissues and Leiomyomas. **J Clin Endocrinol Metab** 58:880-884, 1984.

135. J.J. Miller, G.S. Schultz and R.S. Levy. Rapid Purification of Radio-iodinated Peptides with Sep-Pak Reversed Phase Cartridge and HPLC. **Intl J Peptide Prot Res** 24:112-122, 1984.
136. G.L. Brown, G.S. Schultz, J.R. Brightwell and G.R. Tobin. Biosynthetic Human Epidermal Growth Factor Enhances Epithelial Regeneration. **Surgical Forum** 35: 565-567, 1984.
137. G.S. Schultz, R.E. Galardy and J.D. Jamieson. Biological Activity of an Angiotensin-II-Ferritin Conjugate on Rabbit Aortic Smooth Muscle Cells. **Biochemistry** 20:3412-3418, 1981.
138. G.S. Schultz and Ebner, K.E. Immunological Reactivities of Rat and Human ∀-Lactalbumin. **Compar Biochem Physiol** 67:689-692, 1980.
139. G.S. Schultz, M.P. Sarras, Jr., G.R. Gunther, B.E. Hull, F.S. Gorelick, H.A. Alicea and J.D. Jamieson. Pancreatic Acini Prepared with Purified Collagenase. **Exp Cell Res** 130:49-62, 1980.
140. H.E. Ives, G.S. Schultz, R.E. Galardy and J.D. Jamieson. Preparation of Functional Smooth Muscle Cells from the Rabbit Aorta. **J Exp Med** 148:1400-1412, 1978.
141. A.B. Rawitch, G.S. Schultz, K.E. Ebner and R.M. Vardaris. Competition of)9-Tetrahydrocannabinol with Estrogen in Rat Uterine Estrogen Receptor Binding. **Science** 197:1189-1191, 1977.
142. G.S. Schultz and K.E. Ebner. ∀-Lactalbumin Levels in Human Mammary Tumors, Sera and Mammary Cell Culture Lines. **Cancer Res** 37:4489-4492, 1977.
143. G.S. Schultz and K.E. Ebner. Measurement of ∀-Lactalbumin in Serum and Mammary Tumors of Rats by Radioimmunoassay. **Cancer Res** 37:4482-4488, 1977.
144. B.T. Schroeder, G.S. Schultz, L.W. Walker, B.G. Hudson and K.E. Ebner. Biosynthesis of Lactose by the R3230AC Mammary Tumor in Isolated Cell Culture. **Ann Okla Acad Sci** 4:96-102, 1971.

BOOK CHAPTERS

1. G.A. Chin, R.F. Diegelmann, G.S. Schultz. Cellular and Molecular Regulation of Wound Healing. In: **Wound Healing: Science and Practice**, A. Falabella, and R.S. Kirsner, eds., Marcel Dekker, Inc. New York, NY, USA, in press.
2. G.S. Schultz, G.A. Chin, L.L. Moldawer, R.F. Diegelmann. Principles of Wound Healing. In: **Mechanisms of Vascular Disease: A Textbook for Vascular Surgeons**, M. Thompson, R Fitridge, eds., Greenwich Medical Media Ltd, London UK, in press.
3. S.S. Tuli, M.H. Goldstein, G.S. Schultz. Modulation of Corneal Wound Healing. In: **Cornea**, 2nd edition, J.H. Krachmer, M. J. Mannis and E. J. Holland, eds., Mosby-Year Book, Philadelphia, PA. Chapter 9, in press.
4. G.A. Chin, G.S. Schultz, N. Chegini, R.F. Diegelmann. Biochemistry of Wound Healing. In: **Wound Care Practice,** Paul Sheffield, ed., Best Publishing Co., Flagstaff, AZ, USA, pp. 49-71, 2004.
5. L. Ovington, G.S. Schultz. Physiology of Wound Healing. In: **Chronic Wound Care: A Problem-Based Learning Approach**, M. Morison, L. Ovington, and K. Wilkie, eds., Harcourt Health Sciences, London, UK, pp. 83-100, 2004.
6. G.A. Chin, L.L. Moldawer and G.S. Schultz. Growth Factors, Cytokines and Chemokines. In: **Basic Science for Surgical Specialists**, L.C. Argenta, ed., W. B. Sanders Co., Philadelphia, PA, pp. 25-42, 2004.
7. H.N. Paddock, G.S. Schultz, B.A. Mast. Methods in Re-Epithelialization: A Porcine Model of Partial Thickness Wounds. In: **Wound Healing: Methods and Protocols, Methods of Molecular Medicine**, J.M. Walter, ed., Humana Press, Totowa, NJ, pp. 17-36, 2003.
8. G.S. Schultz. Molecular Regulation of Wound Healing. In: **Acute and Chronic Wounds: Nursing Management, 2nd edition**, R. Bryant ed., Mosby Inc., St. Louis, MO, pp.413-454, 2000.
9. W.C. Parks, G.S. Schultz. Proteases and Protease Inhibitors in Tissue Repair. In: **Peritoneal Surgery**, G. di Zerega, ed., Springer-Verlag, New York, NY, Chapter 7, pp. 101-113, 2000.
10. N.C. Kerr, G.S. Schultz, R.E. Eiferman. Endothelium: Development, Morphology, Disease and Repair. In: **Corneal Surgery: Theory, Technique, and Tissue, 3rd edition**, F.S. Brightwell, ed., Mosby Inc., St. Louis, MO, Chapter 7, pp. 60-72, 1999.
11. G.S. Schultz. Future Developments in Corneal Therapy: Growth Factors. In: **Textbook for Ocular Pharmacology**, T Zimmerman and K Kooner, eds., Raven Press, New York, NY, Chapter 58, pp. 675-679, 1997.
12. G. Rocha, G.S. Schultz. Corneal Wound Healing in Laser In situ Keratomileusis. In: **Advances in Refractive and Corneal Surgery**, M.D. Duplessie, G. Rocha, and J.C. Sanchez-Thorin, eds., Little, Brown and Co., Boston, MA, vol 36, pp. 9-20, 1996.
13. G.S. Schultz. Comparative Tissue Repair. In: **Proceeding of the 3rd International Congress on Pelvic Surgery and Adhesion Formation,** G.S. diZerega, ed., Springer Verlag, New York, NY. Chapter 3, pp. 26-36, 1997.
14. R.W. Tarnuzzer, S.M. Macauley, B.A. Mast, M.C. Stacey, N. Trengove, J. Gibson, L.L. Moldawer, F. Burslem, G.S. Schultz. Epidermal Growth Factor: A Model for the Molecular Pathogenesis of Chronic Wounds. In:

Growth Factors and Wound Healing: Basic Science and Potential Clinical Applications, T.R. Ziegler, G.F. Pierce, and D.N. Herndon, eds., Serono Symposium Inc., Norwall, MA, Chapter 12, pp. 206-228, 1997.

15. G.S. Schultz. Modulation of Corneal Wound Healing. In: **Cornea** J.H. Krachmer, M. J. Mannis and E. J. Holland, eds., Mosby-Year Book, Philadelphia, PA. Chapter 9, 183-198, 1996.
16. G.S. Stern, G.S. Schultz. Pathogenesis of Bacterial Infections of the External Eye. In: **Duane's Foundations of Clinical Ophthalmology**, W. Tasman and E. A. Jaeger, eds., pp. 1-11, 1996.
17. M.B. Sherwood, K. Kato, J.W. Doyle, J.T. Garcia, P.T. Khaw, G.S. Schultz, S. McGorray. Tissue Effects of External Topical Mitomycin-C in Rabbits and its Application to Low Dose Mitomycin-C Therapy. In: **Glaucoma Update,** G.K. Kreiglstein, ed., Verlag Springer, Berlin, Germany. 5:364-371, 1995.
18. R.E. Galardy, M.E. Cassabonne, C. Giese, J.H. Gilbert, F. Lapierre, H. Lopez, M.E. Schaefer, R. Stack, M. Sullivan, R. Summers, R. Tressler, D. Terrell, J. Wee, S.D. Allen, J.J. Castellot, J.P. Barletta, G.S. Schultz, L.A. Fernandez, S. Fisher, T-Y. Cui, H.G. Foellmer, D. Grabelny, W.M. Holleran. Low Molecular Weight Inhibitors of Corneal Ulceration. In: **Inhibition of Matrix Metalloproteinases: Therapeutic Potential**, R.A. Greenwald and L.M. Golub eds., New York Academy of Sciences vol 732, pp. 315-323, 1994.
19. N.C. Kerr, G.S. Schultz, R.E. Eiferman. Endothelium: Development, Morphology, Disease and Repair. In: **Corneal Surgery: Theory, Technique, and Tissue, 2nd edition**, F.S. Brightwell, ed., Mosby Co. St. Louis, MO, pp.52-62, 1993.
20. G.S. Schultz, N.T. Bennett. Growth Factors: Biochemical Characteristics and Roles in Wound Healing. In: **Cytokines and Critical Illness**, A.F. Roach, ed., Report of the 11th Ross Conference on Medical Research, Ross Laboratories, Columbus, OH, pp. 8-13, 1992.
21. S.L.D. MacKay, N.T. Bennett, K.I. Bland, G.S. Schultz. Growth Factors Tumor Suppressor and Cancer. In: **Perspectives in General Surgery**, B.A. Levine, ed. 3:1-25, 1992.
22. G.S. Schultz, D. Twardzik. Assessment Of Biological Activity Of Synthetic Fragments Of Transforming Growth Factor ∀ . In: **Methods in Enzymology**, D Barns, J P Mather, and G H Sato, editors, Academic Press, Inc., New York NY, Vol 198, pp. 200-213, 1991
23. G.S. Schultz. Epidermal growth factor in wound healing. In: **Biological Response Modifiers for Ophthalmic Tissue Repair**, G.R. Grotendorst, L.M. Hjelmeland, and J.P. Gills, editors. Gulf Publishing Co., Houston, TX, pp. 171-182, 1990
24. G. Todaro, G.S. Schultz, D.R. Twardzik, R.A. Eiferman. Tumor Growth Factors and Vaccinia Growth Factors: Role in Epithelial Wound Healing. In: **Development and Disease of Cartilage and Bone Matrix**. Alan R. Liss, Inc., New York, p. 612, 1987.
25. R.A. Eiferman, G.S. Schultz, R.E. Nordquist. Corneal Wound Healing and its Pharmacologic Modification after Refractive Keratotomy. In: **Refractive Keratotomy for Myopia and Astigmatism**, G. O Waring, III ed., C.V. Mosby Co., St. Louis, pp. 749-779, 1991.
26. G.S. Schultz, P.W. Woost, R.A. Eiferman. Modification of Corneal Wound Healing by Growth Factors. In: **The Cornea: Transforming of the World Congress on the Cornea III,** D. Cavanaugh, ed., Raven Press, New York, NY, pp.15-21, 1988.
27. G.S. Schultz, R.A. Eiferman. Human Corneal Endothelial Mitosis and Endothelial Grafting. In: **Corneal Surgery**, F. Brightbill, ed., C.V. Mosby Co., St. Louis, pp. 613-620, 1986.

REVIEW ARTICLES

NOTE: SCIENCE CITATION INDEX LIST 575 CUMULATIVE CITATIONS TO DR. SCHULTZ'S REVIEW ARTICLES IN SEPTEMBER 2000: 5 ARTICLES >50 CITATIONS, 3 ARTICLES >100 CITATIONS, AND 1 ARTICLE >150 CITATIONS.

1. R. Lobmann, G. S. Schultz, H. Lehnert. Proteases and the Diabetic Foot Syndrome - Therapeutic Implications, **Diabetes Care**, in press.
2. G.S. Schultz, D. Barillo, D. Mozingo, G. Chin. Wound Bed Preparation and a Brief History of TIME, **International Wound J**, 1:19-32, 2004.
3. E.A. Ayello, C. Dowsett, G.S. Schultz, G. Sibbald, V. Falanga, K. Harding, M. Romanelli, M. Stacey, L. Teot, W. Vanscheidt. TIME to Prepare the Wound Bed: A New Approach to Chronic Wound Healing, **Nursing 2004**, 34:36-41, 2004.
4. G.A. Chin, G.S. Schultz, M. Stacey. Application of Wound Bed Preparation to Chronic Wound Treatments: TIME to Heal, **Primary Intention**, 11:171-187, 2003.
5. R.G. Sibbald, H. Orsted, G.S. Schultz, P. Coutts, D. Keats. Preparing The Wound Bed 2003: Focus On Infection and Inflammation, **Ostomy Wound Manag**, 49:23-51, 2003.
6. M. Lim, M.H. Goldstein, S.S. Tuli, G.S. Schultz. Growth Factor, Cytokine and Protease Interactions During

Corneal Wound Healing, **Ocular Surface** 1:53-65, 2003

7. G.S. Schultz, G. Sibbald, V. Falanga, E.A. Ayello, C. Dowsett, K. Harding, M. Romanelli, M. Stacey. L. Teot, W. Vanscheidt. Wound Bed Preparation, A Systemic Approach to Wound Bed Management. **Wound Rep Reg** 11 (sup) 1-28, 2003.
8. G. Chin, S. Gowda, G. Schultz. Evaluation of Platelet-Derived Growth Factor in a Rat Model of Ischemic Skin Wound Healing. **Wounds** 14:199-203, 2002.
9. T.D. Blalock, J.C. Varela, S. Gowda, Y. Tang, C. Chen, B.A. Mast, G.S. Schultz. Ischemic Skin Wound Healing Models in Rats. **Wounds**, 13:35-44, 2001.
10. B.A. Mast, G.S. Schultz. Growth Factors and Plastic Surgery. **J Florida Medical Association**, 86:87-91, 2000.
11. A.S. Ågren, W.H. Eaglstein, M.W.J. Ferguson, K.G. Harding, K. Moore, U.K. Saarialjo-Kere, G.S. Schultz. Causes and Effects of the Chronic Inflammation in Venous Leg Ulcers. **Acta Derm Venereol**, suppl 210:3-17, 2000.
12. M.F. Cordeiro, G.S. Schultz, R.R. Ali, S.S. Bhattacharya, P.T. Khaw. Molecular Therapy in Ocular Wound Healing. **Br J Ophthalmol**, 83:1219-1224, 1999.
13. G.S. Schultz, B.A. Mast. Molecular Analysis of the Environment of Healing and Chronic Wounds: Cytokines, Proteases and Growth Factors. **Primary Intention**, 7:7-14, 1999.
14. G.S. Schultz, B.A. Mast. Molecular Analysis of the Environment of Healing and Chronic Wounds: Cytokines, Proteases and Growth Factors. **Wounds: A Compendium of Clinical Research and Practice**, vol 10, Supplement F, 1F-10F, 1998.
15. B.A. Mast and G.S. Schultz. Interactions of Cytokines, Growth Factors, and Proteases in Acute and Chronic Wounds. **Wound Rep Reg** 4:411-420, 1996.
16. R.W. Tarnuzzer, G.S. Schultz. Biochemical Analysis of Acute and Chronic Wound Environments. **Wound Rep Reg** 4:321-325, 1996.
17. P.T. Khaw, N.L. Occleston, G. Schultz, I. Grierson, M.B. Sherwood, G. Larkin. Activation and Suppression of Fibroblast Function. **Eye** 8:188-195, 1994.
18. G.B. van Setten, G.S. Schultz, S.P. Macauley. Growth Factors in Human Tear Fluid and Lacrimal Glands. **Adv Exp Med Biol** 350:315-319, 1994.
19. G.S. Schultz, P.T. Khaw, K.W. Oxford, S.P. Macauley, G.B. van Setten, N. Chegini. Growth Factors and Ocular Wound Healing. **Eye** 8:184-187, 1994.
20. N.T. Bennett, G.S. Schultz. Growth factors and wound healing: Part II. Role in Normal and Chronic Wound Healing. **Am J Surgery** 166:74-81, 1993.
21. N.T. Bennett, G.S. Schultz. Growth factors and Wound Healing: Part I. Biochemical Properties of Growth Factors and Their Receptors. **Am J Surgery** 165:728-737, 1993.
22. G.S. Schultz, N. Chegini, M. Grant, P.T. Khaw, S.L.D. MacKay. Effect of Growth Factors On Corneal Wound Healing. **Acta Ophthalmologica**, 70:60-66, 1992.
23. G.S. Schultz, M.B. Grant. Neovascular Growth Factors. **Eye** 5:170-180, 1991.
24. G.S. Schultz, D.S. Rotatori, W. Clark. EGF and TGF-∀ in Wound Healing and Repair. **J Cell Biochem** 45: 346-352, 1991.
25. G.S. Schultz, J.B. Davis, R.A. Eiferman. Growth Factors and Corneal Epithelium. Cornea 7:96-101, 1988.

SUBMITTED PUBLICATIONS

1. L.J. McKenzie, G.S. Schultz, R.S. Williams, N.M. Dean, J.C. Varela, N. Chegini. Inhibition of Surgical Adhesions by Antisense Oligonucleotide to TGF1. Submitted
2. G.B van Setten, T Blalock, G. Grotendorst, G.S. Schultz, A. Westermark. Detection of Connective Tissue Growth Factor in Orbito-Facial Pathology. Submitted to Orbit.
3. R. Lobmann, G. Schultz, H. Lehnert. Molecular basis of wound healing in the diabetic foot syndrome. Submitted to Daibetes Care

ARTICLES IN PREPARATION

1. C. Chen, B. Michelini-Norris, S. Stevens, J. Rowsey, X. Ren, M. Goldstein, and G.S. Schultz. Quantitative Measurement of mRNAs for EGF, TGF-a, and EGF Receptor in Rat Corneas After PRK. In preparation
2. R. Leng, N. Chegini, B. Michelini-Norris, J. Rowsey, M. Goldstein, and G.S. Schultz. Immunolocalization of TGF Isoforms, TGF-II Receptor, EGF and EGF-R in Rat Corneas After PRK. In preparation
3. R. Yuan, Xio-ou Ren, T.D. Blalock, J.C. Varela, A.S. Lewin, and G.S. Schultz. Kinetic and *In Vitro* Cell Analysis of a Hammerhead Ribozyme Targeting Transforming Growth Factor Beta-1. In preparation
4. T.D. Blalock, H.V. Baker, S.S. Tuli, G.S. Schultz. Connective Tissue Growth Factor Regulation of Gene Expression in Human Corneal Fibroblasts, in preparation.

5. T.D. Blalock, H. MacArthur, G.R. Grotendorst, S.S. Tuli, M.W.J. Ferguson, and G.S. Schultz. Mannose-6 Phosphate/Insulin Like Growth Factor II Receptor Binds CTGF and Mediates Its Action on Human Corneal Fibroblasts, Submitted
6. K.B. Kim, L. Coffey, M. Goldstein, G.S. Schultz, D.W. Hahn. Analysis Of Dense Medium Light Scattering With Applications To Corneal Tissue: Experiments And Monte Carlo Simulations, submitted.
7. S.S. Tuli, R. Liu, T.D. Blalock, C. Chen, M.H. Goldstein, G.S. Schultz. Immunohistochemical Localization of TGF-a, TGF-b, EGF, and their Receptors in Rat Corneas Following PRK Ablation, in preparation.

MAJOR INVITED PRESENTATIONS

1. Identifying and Correcting the Molecular Imbalances in Chronic Wounds, World Union of Wound Healing Societies, Paris France, July 9, 2004.
2. Stem Cells in Wound Healing, Program Organizer, Symposium on Advance Wound Care, Orlando, FL, May 2, 2004.
3. Scientific Basis for Wound Bed Preparation, Wounds UK 2003, Harrogate, United Kingdom, November 12, 2003.
4. MMPs – Current Developments in Wound Biology, European J & J Wound Symposium, Hamburg, Germany, October 14 -15, 2003.
5. Future Developments in Wound Care, Innovations Seminar, Smith & Nephew, York, UK, September 25, 2003.
6. Wound Bed Preparation, European Tissue Repair Society, Amsterdam, Netherlands, September 22, 2003.
7. Scar Wars: Regulation of Ocular Scarring, Bascom Palmer Eye Institute, University of Miami, May 1, 2003.
8. Understanding the Chronic Wound, Symposium on Advanced Wound Care, Las Vegas, NV, April 28, 2003.
9. Molecular Approaches in the Treatment of Ulcerative Keratitis, Thygeson Lectureship, Ocular Microbiology and Immunology Group meeting, October 19, Orlando , FL, 2002.
10. Molecular Characterization of Acute and Chronic Wounds, 4th Australian Wound Management Association Meeting, Adelaide, Australia, March 7, 2002
11. Molecular Approaches to Regulating Ocular Wound Healing, 11th Annual European Tissue Repair Conference, Cardiff, Wales, UK, September 5, 2001
12. mRNA Responses in Rat Corneas After PRK, M. Goldstein, and G.S. Schultz, XIV International Congress of Eye Research, Santa Fe, NM, October 15-18, 2000
13. Molecular Pathophysiology of Venous Ulcers. 1st World Wound Healing Congress, Melbourne, Australia, September 11-13, 2000
14. Cytokines and Proteases in Acute and Chronic Wounds. 8th Annual Meeting of the European Tissue Repair Society, Copenhagen, Denmark, August 27, 1998.
15. Protease and Inhibitors in Corneal Wound Healing, XIII International Congress of Eye Research, Paris, France, July 27, 1998.
16. Molecular Pathophysiology of Chronic Wounds, Association of Advanced Wound Care Symposium, Miami, April 21, 1998.
17. Molecular Regulation of Wound Healing, Florida Wound Care Symposium, Gainesville, FL, February 7, 1998.
18. Gene Therapy For Acute and Chronic Wounds, Australian Wound Management Association Meeting, Brisbane, Australia, January 10, 1998.
19. Biochemical Analysis of Acute and Chronic Wounds, University of Miami, October 3, 1997.
20. Growth Factors and Wound Healing, 1st Ethicon Endo-Surgery Lectureship, American Society for Reproductive Medicine, October 21, 1997, Cincinnati, OH.
21. Corneal Wound Healing, Everett Kinsey Lecture at the annual meeting of the Contact Lens Association of Ophthalmologist, Las Vegas NV, January 16 to 18, 1997.
22. Regulation of Corneal Wound Healing by Growth Factors, Keystone Symposium on Ocular Cell and Molecular Biology, Tamarron, Colorado, January 7 to 12, 1997.
23. Differential Expression of Cytokines in Acute and Chronic Human Wounds, 4th International Congress on The Immune Consequences of Trauma, Shock, and Sepsis, March 4 to 8, 1997, Munich, Germany.
24. 3rd International Congress on Pelvic Surgery and Adhesion Prevention, February 29, 1996, San Diego, CA.
25. Modulation of Corneal Wound Healing, Oxford Ophthalmic Congress, Oxford, UK, July 2-5, 1995.
26. Modulation of Corneal Wound Healing, Joseph M. Bryan Lecturer, Duke University, January 11, 1995.
27. Protease Levels in Healing and Chronic Human Wounds. Protease and Adhesion Molecules in the Pathophysiology and Treatment of Cancer, Inflammation/Coagulation and Skin Disorders, Brodo/Ljubljana, Slovenia, June 4-8, 1994.
28. Biochemical Analysis of Human Wound Fluids. Fourth Annual Research Forum on Wound Repair, University of Miami, April 28 to May 1, 1994.
29. Biochemical Analysis of Human Wound Fluids. Medical and Dental College of New Jersey, University of New

Jersey, January 5, 1994.

30. Growth Factors and Proteases in Ocular Wound Healing. Singapore Nation Eye Center, December 13, 1993.
31. Growth Factors and Ocular Wound Healing. XXIII Cambridge Ophthalmology Symposium, September 9-10, 1993.
32. EGF and TGF-∀ Wound Repair, UCLA Conference on Progress in Basic Research of Wound Repair and its Application to Clinical Management of Problem Wounds. Breckenridge, CO. April 3, 1993.
33. The Use of Growth Factors in Promoting Wound Healing, Washington State Ophthalmological Society Meeting, Seattle, WA, September 21, 1991.
34. Growth Factors and Ocular Wound Healing, Wound Healing of the Ocular Surface & Paulo Foundation International Medical Symposium, Helsinki, Finland, August 25-28, 1991.
35. EGF and Wound Therapy, UCLA Symposium on Wound Repair. Keystone, CO April 7, 1991.
36. Growth Factors, 15th Clinical Congress of the American Society of Parenteral and Enteral Nutrition, San Francisco, CA, January 26, 1991.
37. Overview of Growth Factors and Wound Healing II, Technology Management Group, Boston, MA, December 6-7, 1990.
38. Neovascular Growth Factors, Cambridge Ophthalmological Symposium, St. John's College, Cambridge, England, September 17-19, 1990.
39. EGF and its Receptor in Cornea and Wound Healing. University of Kansas, April 5, 1990.
40. EGF and TGF-∀ in Wound Healing and Repair, UCLA Symposium on Tissue Engineering, Key Stone, CO., April 6-12, 1990.
41. Overview of Growth Factors in the Eye, Annual Meeting of the Association for Research in Vision and Ophthalmology Association, Sarasota, Florida, April 30, 1989.
42. EGF in Corneal Wound Healing, Visions in Wound Healing, March 16-18, 1988 Innisbrook, Florida.
43. Biosynthetic Growth Factors and Wound Healing, Industrial Biotechnology Association, February 16-18, 1988, Naples, Florida.
44. Modulation of Corneal Wound Healing by Growth Factors, Emory University, September 16, 1988
45. Transforming Growth Factor-Alpha (TGF-∀) and its Receptor in Neural Retina. Eight International Congress for Eye Research, San Francisco, September 4-8, 1988.
46. Development of Epidermal Growth Factor and Its Uses in Wound Healing. Growth Factors for Wound Healing, symposium sponsored by Technology Management Group, Inc., New Haven, CT, November 1-3, 1988.
47. Candidate Agents to Enhance Wound Healing. American Society of Cataract and Refractive Surgery, Los Angeles, CA, March 29, 1988.
48. Molecular Mechanism of Regeneration of Wound Healing by Growth Factors. Memorial Sloan-Kettering Cancer Center, New York, NY, February 26, 1988.
49. Topical Epidermal Growth Factor. Castroviejo Society Symposium, Las Vegas, January 14, 1988.
50. Drugs That Modify Corneal Wound Healing. World Congress on the Cornea III, Washington, D.C., April 27-May 1, 1987.
51. Effect of Growth Factors in Keratorefractive Surgery. World Refractive Surgery Symposium, Rome, Italy, May 2-4, 1986.
52. Pre-Clinical Application of Biosynthetic EGF. American Tissue Culture Association. Ohio Valley Branch, Columbus, OH, April 3, 1986.
53. Hormonal Regulation of Wound Healing, Collagen Corp., San Francisco, CA, June 1, 1985.
54. Human Corneal Endothelial Cell Mitosis and Endothelial Grafting - Is it Possible in Corneal Surgery and Eye Banking. First International Cornea and Eye Banking Symposium, San Diego, CA, June 4-8, 1985.
55. Action of Growth Factors on Corneal Wound Healing. Sixth International Congress for Eye Research, Alicante, Spain, October, 1984.
56. Acceleration of Corneal Wound Healing by Biosynthetic Human EGF. University of Oklahoma, Department of Ophthalmology, March 26, 1984.
57. Role of EGF and TGF in Breast Cancer. Oncogen, March 20, 1984.
58. A Mini Symposium on Potential Application of EGF in Surgery. Chiron Corporation, February 20, 1984.
59. Peptide Growth Factors: Comparison of in vitro and in vivo effects. Ohio Valley Tissue Culture Association, Miami University, October, 1983.
60. Symposium on Renin-Angiotensin System: Enzymology, Receptor and its Role in Understanding Hypertension. University of Kentucky, April 20, 1981.

LECTURES AT THE UNIVERSITY OF LOUISVILLE

1. **Medical Biochemistry 600.** Presented lectures, from 1979 to 1989, on water, pH, amino acids, protein structure and purification, collagen, elastin, contractile proteins, blood clotting, antibodies, simple carbohydrates, proteoglycans, glycoproteins, and endocrinology. Course director, first quarter, 1984.

2. **Biochemical Endocrinology 670.** Initiated this new graduate course required for Ph.D. students in Biochemistry in 1980. Presented lectures in 1980, 81, 82, 83 on pituitary hormones including gonadotrophins, prolactin, growth hormone, ACTH, and on endorphins, growth factors, oncogenes, catecholamines, insulin, glucagon, gastrointestinal hormones and angiotensin. In 1984 this course was enlarged to include topics of advanced reproductive endocrinology including placental hormone production, immune system hormones, and biochemical aspects of in vitro fertilization/embryo transfer. Course director 1980-1988.

3. **Biochemical Methods 612.** Presented lectures, from 1979 to 1988, on radioisotopic techniques, and on cell and tissue culture techniques.

4. **Special Topics in Biochemistry 603.** Presented lectures in 1981, 82 on glycoprotein biosynthesis, and intracellular compartmentalization of proteins.

5. **Board Review Course BRC-84.** Presented review lectures on protein chemistry, hemoglobin, blood clotting and enzymology for sophomore students taking National Boards, Part I.

RESEARCH INSTRUCTION AT UNIVERSITY OF LOUISVILLE

1. Primary Advisor	Year	Current Position
Susan Fitzpatrick, M.S.	1980	Faculty member, Baylor University
William King, M.S.	1986	Resident in Surgery, University of Louisville
Philip Woost, Ph.D.	1987	Postdoctoral Associate, Case Western University
Glenn Franklin, M.S.	1988	Resident in Surgery, Medical College of Georgia
John Henry, Ph.D.	1989	Boston Biomedical Research Institute

2. Dissertation or Thesis Committees	Year	Department
Ronald Wiehle, Ph.D.	1983	Biochemistry
Georgette Howard, Ph.D.	1986	Biochemistry
James Miller, Ph.D.	1987	Biochemistry
Steve Wagner, Ph.D.	1986	Biochemistry
Raymond Weckman, M.S.	1983	Anatomy
Melinda Brown, Ph.D., MD	1984	Anatomy
Nancy Muma, Ph.D.	1985	Pharmacology
Deanne Benovitz, Ph.D.	1986	Chemistry
Douglas Sherman, Ph.D.	1988	Chemistry
Patricia Drury, M.S.	1988	Anatomy

3. Postdoctoral Associates	Year	Current Position
Michael P. LaChance, MD, Ph.D.	1982	Private practice
Gerry O'Daniel, MD	1986	Private practice
Nancy Muma, PhD	1985	Pharmaceutical industry
Mindy Brown, Ph.D., MD	1985	Private practice
Elaine Sonnenfeld, Ph.D.	1986	Pharmaceutical industry
Mark Petitjean, MD	1987	Private practice
Krzysztof Darlak, Ph.D.	1987-88	Peptides International, Inc.
Shawn Jones, M.D.	1987-88	Private practice

4. Research Assistant Professor

Dr. Ming Ling, 1983, currently Chairman of Biochemistry, National University of Taiwan

5. Medical/Dental Students: Summer Research Program or Research Elective

Larry Williams, M.D.	1983	Lisa Cipolla, M.D.	1987
Joseph Metz, DMD	1983	Angela Duff, M.D.	1987
Mark Lambertus, M.D.	1984	Allan Whitehouse, M.D.	1987
Jerry Schrodt, M.D.	1985	Robert Mitchell, M.D.	1988
Joseph Brightwell, M.D.	1985	Jerry Davis, M.D.	1988
Steve Riddle, M.D.	1986	E. Brit Brockman, M.D.	1988
John Fassio, M.D.	1989		

6. Undergraduate Summer Research Scholars

1. Jamie Monroe	1983
2. Mary Lorenz	1980
3. Melissa Roberts	1987

7. Awards Recognizing Research of Graduate or Medical Students

Philip Woost	Yankeelov Award for Outstanding Ph.D. student in Biochemistry, 1984; First Place, Student Research Day Competition, 1983; Graduate and Professional Student Research Awards, 1982 and 1983; American Cancer Society Institutional Award, 1983-84
Lisa Cipolla	Second Place, Student Research Day Competition, 1984
Angela Duff	Honorable Mention, Student Research Day Competition, 1984
Steve Riddle	Second Place, Student Research Day Competition, 1983
Jerry Schrodt	Honorable Mention, Student Research Day Competition, 1982

CLASSROOM INSTRUCTION AT THE UNIVERSITY OF FLORIDA

1. **BMS 5204 Medical Biochemistry.** Teach ten clinical correlation discussions for a unit lab of freshman medical students from 1991 to present.

2. **GM 6161 Oral Biology II.** Teach one lecture on general principles of wound healing to oral biology graduate students and post-graduate dental fellows from 1995 to present.

3. **DEN 6657 Introduction to Advanced Periodontology.** Teach three lectures on the principles of wound healing to oral post-graduate periodontology fellows from 1996 to present.

4. **GMS 6001 Interdisciplinary Graduate Program Core Course.** Teach two lectures and one discussion session on the components of the extracellular matrix in 1998-2000.

5. **Dentistry 6128 Principles of Immunology.** Teach three lectures on the principles of wound healing to second year dental students from 1999- to present.

RESEARCH INSTRUCTION AT UNIVERSITY OF FLORIDA

1. PRIMARY ADVISOR	PROGRAM	AREA	DEGREE	YEAR
Vivian Chen, M.S.	MS Program	Molecular Genetics	M.S.	1998
Cui Chen, M.S.	IDP Program	Cell Biology	M.S.	1999
Glenn Ladwig, L.L.D.	MS Program	Molecular Genetics	M.S.	2000
Lakshmi Balasubramanian, M.B.B.S.	MS Program	Molecular Genetics	M.S.	2000
Santosh Gowda, M.B.B.S.	MS Program	Molecular Genetics	M.S.	2002
Heather Paddock, M.D.	APPCI	Clinical Investigation	M.S.	2002
Tim Blalock, B.S.	IDP Program	Molecular Genetics	Ph.D.	2003
Suresha Rajaguru, M.B.B.S.	MS Program	Molecular Genetics	M.S.	2004
Jia Liu, B.S.	PhD Program	Molecular Genetics	Ph.D.	candidate
Heejung Yang	MS Program	Molecular Genetics	M.S.	candidate

2. M.S. & Ph.D. Dissertation Committees

	Department	Degree	Year
James Talton, M.S.	Material Sciences	M.S.	1995
Shawn P. Macauley, Ph.D.	Oral Biology	Ph.D.	1996
Susan Rassmussen, Ph.D.	Chemistry/Biochemistry	Ph.D.	1997
Robert Habda, M.S.	Material Sciences	M.S.	1997
Ho-Seng Kim, Ph.D.	Pharmaceutical Sciences	Ph.D.	1998
Adriana Da Silveira, Ph.D.	Oral Biology	Ph.D.	1998
Sharon Wall, Ph.D.	Neuroscience	Ph.D.	1998
James Talton, Ph.D.	Pharmaceutics	Ph.D.	1999
Larry Land, Ph.D.	Chemistry	Ph.D.	2001
Toby Ferguson, Ph.D., M.D.	Neuroscience	Ph.D.	2000
Harveen Dhillon, Ph.D.	Neuroscience	Ph.D.	2000
Sonja Parisek, M.S.	Animal Sciences	M.S.	2001
Jing Li, M.S.	Molecular Genetics	M.S.	2003
Mihai Ciustea, B.S.	Chemistry	Ph.D.	2003
Kareem Burney, B.E.	Biomedical Engineering	M.S.	2003
Taili Thula, B.E.	Biomedical Engineering	M.S.	2003
Franck Ollivier, DVM	Animal Sciences	Ph.D.	2004
Rong Xiu, B.S.	Molecular Genetics	M.S.	2004
Beverly Childress, B.S.N.	Nursing	Ph.D.	2004
John Azeke, B.E.	Biomedical Engineering	Ph.D. candidate	
Tara Washington, B.E.	Biomedical Engineering	Ph.D. candidate	
Olajompo Moloye, B.E.	Biomedical Engineering	Ph.D. candidate	
Kareem Burney, B.E., M.S.E.	Biomedical Engineering	Ph.D. candidate	
Taili Thula, B.E., M.S.E.	Biomedical Engineering	Ph.D. candidate	
Lee Ferguson, B.S.	Molecular Genetics	Ph.D. candidate	

3. External Examiner

Rijian Wang, Ph.D.	1997	University of Alberta, Edmonton, Canada Department of Surgery

4. Residents Research Projects

Ophthalmology	Year	Surgery	Year	Otolaryngology	Year
Scott Strelow, M.D.	1989	Scott Rotatori, M.D.	1989	Jonathan King, M.D.	1990
Natalie Kerr, M.D.	1990	Neil Bennett, M.D.	1990	Agnes Nall, M.D.	1992
John Barletta, M.D.	1992			Hugh Sims, M.D.	1992
Karen Oxford, M.D.	1992			Warren Stiles, M.D.	1992
Kelly Hutcheson, M.D.	1995			Peyton Colvin, M.D.	1993
Mario Forcina, M.D.	1996			Mike Avidono, M.D.	1993
Guy Angella, M.D.	1997			Cheryl Cotter, M.D.	1993
John Gross, M.D.	2002			Jason Wilmoth, M.D.	1998

6. Medical Students Research Electives

Lee Jung, 1990	Kyle Balch, 1992	David Kimble, 1992	Robert Stiff, 1994	Jeff Brink, 1990
Ken Haft, 1992	Tuan Nguyen, 1993	Missy Block, 1996	Steve Tebes, 1997	

7. Post Doctoral Associate

	Years	Current Position
Sally MacKay, Ph.D.	1991-4	Assistant Professor, Dept Surgery, Univ. Florida
Roy Tarnuzzer, Ph.D.	1993-6	Assistant Professor, Dept Medicine, Univ. Florida
Xiao-ou Ren, M.D., Ph.D.	1996-8	Post-Doctoral Associate, University of North Carolina
Rong Yuan, M.D., Ph.D.	2000-1	Research Associate, Cold Springs Harbor Labs

8. High School Students and Science Teachers

Tuan Lui	1995	Summer Scientists Training Program	Miami High School, Miami, Florida
David Mills	1996	Summer Scientists Training Program	Deltona High School, Deltona, Florida
Lan Van	1997	Summer Scientists Training Program	Miami High School, Miami, Florida
Dan Foster	1997	Teacher Research Update Experience	Powell High School, Knoxville, TN
Sun Hee Rim	1998	Summer Scientists Training Program	Hillsborough High School, Hillsborough, Florida
Jessica Prenatt	1998	Teacher Research Update Experience	Lovejoy Middle School, Lovejoy, GA

Pamela Smith	1998	Teacher Research Update Experience	Johnson Middle School, Jacksonville, FL
Albert Huang	1999	Summer Scientists Training Program	Spruce Creek High School, Ormond Beach, FL
Vandana Gupte	1999	Teacher Research Update Experience	Hedgesville High School, Hedgesville, WV
Alicia Wright	2000	Summer Scientists Training Program	Vanguard High School, Ocala, Florida
Mindy Pearson	2000	Teacher Research Update Experience	Rodgers Middle School, Riverview, Florida
Vikram Palker	2001	Summer Scientists Training Program	Anderson High School, Ft. Lauderdale, Florida
Cynthia Vasques	2002	Summer Scientists Training Program	Boca Raton High School, Florida
David Reyes	2003	Summer Scientists Training Program	Blanche Ely High School, Pompano Beach, FL
Craig Levoy	2004	Summer Scientists Training Program	Spruce Creek High School, Ormond Beach, FL
Philip Carlson	2004	Summer Scientists Training Program	Christopher Columbus High School, Miami, FL

9. SENIOR UNDERGRADUATE HONORS RESEARCH PROJECTS

Eric Kohlbrenner	1998	Senior Research
Juan Varela	1999	University Scholar Program
Kelly Brinsko	2000	University Scholars Program
Kavita Gandhi	2001	University Scholars Program
Sima Patel	1999	Senior Research
Brett Baschovitz	2003	Senior Research

SERVICE AT THE UNIVERSITY OF LOUISVILLE

COLLEGE OF MEDICINE

Committee	Year
1. Medical Student Grievance Committee	Member 1981-1986, Chair, 1983-86
2. Freshman Medical Student Unit Laboratory Advisor	Member 1982-84
3. J. G. Brown Cancer Center, Oncology Seminar Committee	Chair, 1983-84
4. J. G. Brown Cancer Center, Education Committee	1982
5. Medical Student Promotions Committee	1984
6. President's Distinguished Teaching Award, Medical Center	Nomination Committee, 1984-86
7. Pharmacology Graduate Program Review Committee	Chair, 1985

Biochemistry Department

1. Search Committee for Assistant Professor positions, 1981, 82, 86, 87 (Chair)
2. Director of Undergraduate Summer Research Program, 1980
3. Graduate Committee, 1979-87
4. Personnel Committee, 1984, 86, 87
5. Research Committee, 1984, 86, 87
6. Co-organizer of Research Conference, "Biochemistry of Ligand-Protein Interaction" 1979

Associate Appointments

1. Department of Ophthalmology, 1984
2. Department of Obstetrics and Gynecology, 1984
3. Department of Surgery, 1984

SERVICE AT THE UNIVERSITY OF FLORIDA

General Committees

1. Clinical Research Center, Review Committee, 1989-91
2. University of Florida Faculty Senate, 1991-1992
3. Faculty Council, Ob/Gyn Department Representative, School of Medicine, 1994-95
4. Faculty Council, Vice President, School of Medicine, 1995-96
5. Basic Science Reorganization Faculty Advisory Committee, October, 1995
6. Faculty Council, President, 1997-98
7. Faculty Research Advisory Board, 1996-99
8. Sexual Harassment Committee, 2000-present
9. Medical Student Admission Committee, 2002-2005
10. Faculty Council Secretary, 2003-2006

11. University Academic Freedom, Tenure, Professional Relations and Standards Committee, 2004-

Faculty Search Committees
1. Chair, Department of Biochemistry, May, 1995
2. Assistant Professor, Structural Biologist, Department of Ophthalmology, July 1995
3. Assistant Research Scientist, Department of Otolaryngology, August 1995.
4. Assistant Professor, Department of Physiology, 1997
5. Chief of Plastic Surgery, Department of Surgery, 2004
6. Chair, Department of Dermatology, 2004

Adjunct Faculty Appointments
1. Department of Biochemistry, 1992
2. Department of Medicine, 1992
3. Department of Ophthalmology, 1989
4. Department of Oral Biology, 1995

SERVICE FOR SCIENTIFIC ORGANIZATIONS

Scientific Organizations
1. Program Planning Committee, Association for Research in Vision and Ophthalmology, Cornea, 1988-1991
2. Board of Directors, Wound Healing Society, 1995-97.
3. Program Planning Committee, 2nd Joint Meeting of Wound Healing Society and European Tissue Repair Society, Boston MA, May, 1996.
4. President-Elect of Wound Healing Society, 1997-98
5. President of Wound Healing Society, 1999-01
6. Past President of Wound Healing Society, 2000-2002

Ad Hoc Reviewer
Journals
1. American Journal of Surgery
2. American Journal of Physiology
3. American Journal of Pathology
4. Biochemica et Biophysica Acta
5. Breast Cancer Research and Treatment
6. British Journal of Ophthalmology
7. Cancer Research
8. Cell and Molecular Biology
9. Comparative Biochemistry and Physiology
10. Current Eye Research
11. Diabetologia
12. Diabetes Care
13. Endocrinology
14. Experimental Eye Research
15. Federation Proceedings
16. Infection and Immunity
17. Investigative Ophthalmology and Visual Science
18. Journal of Investigative Dermatology
19. Journal of Histochemistry and Cytochemistry
20. Journal of Surgical Research
21. Journal of Interferon Research
22. Journal of Vascular Surgery
23. Molecular Pharmacology
24. Molecular and Cellular Biochemistry
25. Proceedings of the National Academy of Science
26. Regulatory Peptides
27. Society for Experimental Biology and Medicine
28. Wound Repair and Regeneration

Editorial Board
Executive Editor for Experimental Eye Research, 1997 – present
Editorial Board for Current Eye Research, 2001 – present
Cutaneous and Ocular Toxicology, 2001 – present
Primary Intention, Australian Wound Management Association, 2002 – present
Wound Repair and Regeneration, 2002 – present
International Wound Journal, 2003 – present
International Journal of Lower Extremity Ulcers, 2004 – present

Reviewer for Grant Agencies
1. Kentucky Heart Association 1985
2. National Science Foundation 1986
3. NIH Vision 1 Study Section Ad Hoc member 1988
4. NIH Institute of Arthritis Musculoskeletal Disease Ad Hoc member 1991

5. NIH Clinical Sciences 1 Study Section Ad Hoc member 1992
6. Tobacco and Health Research 1988
7. W. W. Smith Charitable Trust 1992
8. Wellcome Trust, Ltd 1993
9. NIH Arthritis, Connective Tissue and Skin Study Section Ad Hoc member 2004

Patents Awarded and Submitted

1. Promotion of Corneal Stroma Wound Healing With Human Epidermal Growth Factor Prepared From Recombinant DNA. Inventors: G.S. Schultz, R.A. Eiferman, G.L. Brown, assigned to University of Louisville, and P. Valenzuela, assigned to Chiron Corporation, U.S. Patent No. 4,959,353, issued September 25, 1990.
2. Treatment for Tissue Ulceration. Inventors: R.E. Galardy, D. Grobelny, G.S. Schultz assigned to University of Florida. U.S. Patent No. 5,114,953, issued May 19, 1992.
3. Treatment for Tissue Ulceration. Inventors: R.E. Galardy, D. Grobelny, G.S. Schultz assigned to University of Florida. U.S. Patent No. 5,270,326, issued December 14, 1993.
4. Method for Treating Corneal Endothelial Wounds. Inventors: G.S. Schultz, assigned to University of Florida and R.W. Shimuzu assigned to Chiron Vision. U.S. Patent No. 5,310,728, issued May 10, 1994.
5. Synthetic Matrix Metalloproteinase Inhibitors and Use Thereof. Inventors: R.E. Galardy, D. Grobelny, G. Schultz assigned to University of Florida. U.S. Patent No. 5,773,438, issued June 30, 1998.
6. Process for Preparing Synthetic Matrix Metalloprotease Inhibitors. Inventors G. Schultz, assigned to the University of Florida. U.S. Patent No. 5,892,112; issued April 6, 1999.
7. Medical Use of Metalloproteinase Inhibitors for Inhibiting Tissue Contraction. Inventors: P.T. Khaw, assigned to University of London, and G.S. Schultz assigned to University of Florida. U.S. Patent No. 6,093,398 issued July 25, 2000.
8. Medical Use of Metalloproteinase Inhibitors for Inhibiting Tissue Contraction. Inventors: P.T. Khaw, assigned to University of London, and G.S. Schultz assigned to University of Florida. U.S. Patent No. 6,379,667 issued April 30, 2002.
9. Cosmetic Composition and Method. Inventors: G.S. Schultz, assigned to University of Florida, and D.S. Lerner, assigned to QuickMed Technologies. US Patent No. 6,713,074, issued March 30, 2004.
10. Intrinsically Bactericidal Absorbent Dressing and Method of Fabrication. Inventors: C.D. Batich, G.S. Schultz, B.A. Mast, assigned to University of Florida, G.M. Olderman, D. Lerner, assigned to QuickMed Technologies, Australian Patent No. 773532, issued May 27, 2004.
11. Medical Use of Metalloproteinase Inhibitors for Inhibiting Tissue Contraction. Inventors: P.T. Khaw, assigned to University of London, and G.S. Schultz assigned to University of Florida. U.S. Patent No. 6,759,432 B2, issued July 6, 2004.
12. Composition and Method for Minimizing or Avoiding Adverse Effects of Vesicants. Inventors D. S. Lerner, assigned to QuickMed Technologies, and G. S. Schultz, assigned to University of Florida. US Patent Application 2003/0083321 A1, submitted September 25, 2002.

Consultant Activities

Chiron, Inc.	Chiron Vision	Ethicon, Inc.	U.S. Biomaterials	Santen Inc.
Oncogen, Inc.	Glycomed, Inc.	Vistacon, Inc.	Anamed, Inc.	Thermogenesis, Inc.
Arriva Pharmaceuticals	Quick Med, Inc.	Fibrogen, Inc.	Renovo, Ltd.	Greystone Medical, Inc.

Clinical Trials

1. Accelerated Corneal Epithelial Wound Healing using Human Epidermal Growth Factor after Corneal Transplantation. June 1, 1984.
2. Use of Human Epidermal Growth Factor in Severe Corneal Epithelial Defects. June 10, 1984.
3. Use of Biosynthetic Human Epidermal Growth Factor for Accelerating Epidermal Healing of Split-Thickness Donor-Sites of Burn Patients. June 2, 1986.
4. Treatment of Diabetic Foot Ulcers with a Protease Inhibitor, Doxycycline, October 1, 2001.
5. Treatment of Diabetic Foot Ulcers with an Adenovirus Vector expressing PDGF, August, 2002.

PDR®

54

EDITION

2000

PHYSICIANS' DESK REFERENCE®

Senior Vice President, Directory Services: Paul Walsh

Director of Product Management: Mark A. Friedman
Associate Product Manager: Bill Shaughnessy
Senior Business Manager: Mark S. Ritchin
Financial Analyst: Wayne M. Soltis
Director of Sales: Dikran N. Barsamian
National Sales Manager, Pharmaceutical Sales: Anthony Sorce
National Account Manager: Don Bruccoleri
Senior Account Manager: Frank Karkowsky
Account Managers:
Marion Gray, RPh
Lawrence C. Keary
Jeffrey F. Pfohl
Suzanne E. Yarrow, RN
Electronic Sales Account Manager: Stephen M. Silverberg
National Sales Manager, Medical Economics Trade Sales: Bill Gaffney
Director of Direct Marketing: Michael Bennett
List and Production Manager: Lorraine M. Loening
Senior Marketing Analyst: Dina A. Maeder

Director, New Business Development and Professional Support Services: Mukesh Mehta, RPh
Manager, Drug Information Services: Thomas Fleming, RPh
Drug Information Specialist: Maria Deutsch, MS, RPh, CDE
Editor, Directory Services: David W. Sifton
Senior Associate Editor: Lori Murray
Director of Production: Carrie Williams
Manager of Production: Kimberly H. Vivas
Senior Production Coordinator: Amy B. Brooks
Production Coordinators: Gianna Caradonna, Maria Volpati
Data Manager: Jeffrey D. Schaefer
Senior Format Editor: Gregory J. Westley
Index Editors: Johanna M. Mazur, Robert N. Woerner
Art Associate: Joan K. Akerlind
Senior Digital Imaging Coordinator: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Electronic Publishing Designer: Livio Udina
Fulfillment Manager: Stephanie DeNardi

Officers of Medical Economics Company: *President and Chief Executive Officer:* Curtis B. Allen; *Vice President, New Media:* L. Suzanne BeDell; *Vice President, Corporate Human Resources:* Pamela M. Bilash; *Vice President and Chief Information Officer:* Steven M. Bressler; *Chief Financial Officer:* Christopher Caridi; *Vice President and Controller:* Barry Gray; *Vice President, New Business Planning:* Linda G. Hope; *Vice President, Business Integration:* David A. Pitler; *Vice President, Finance:* Donna Santarpia; *Senior Vice President, Directory Services:* Paul Walsh; *Senior Vice President, Operations:* John R. Ware; *Senior Vice President, Internet Strategies:* Raymond Zoeller

Printed on recycled paper

ISBN: 1-56363-330-2

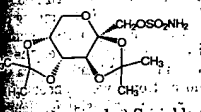
maceutical, McNEIL AB, Inc.
PA 19477
1997 643-10-089-2
Product Identification Guide, page 329

℞

AX®
e)
o capsules)
apsules

PTION

is a sulfamate-substituted monosaccharide that
d for use as an antiepileptic drug. TOPAMAX®
capsules) Sprinkle Capsules are available as 15
mg sprinkle capsules for oral administration as
ules or for opening and sprinkling onto soft food.
is a white crystalline powder with a bitter taste.
is most soluble in alkaline solutions containing
hloride or sodium phosphate and having a pH of
is freely soluble in acetone, chloroform, dimeth-
, and ethanol. The solubility in water is 9.8 mg/
trated solution has a pH of 6.3. Topiramate has
ular formula $C_{12}H_{21}NO_8S$ and a molecular weight
Topiramate is designated chemically as 2,3:4,5-
opylidene-β-D-fructopyranose sulfamate and has
ing structural formula:



AX (topiramate capsules) Sprinkle Capsules con-
ramate coated beads in a hard gelatin capsule. The
gredients are: sugar spheres (sucrose and starch),
ellulose acetate, gelatin, silicone dioxide, sodium
ate, titanium dioxide, and black pharmaceutical

AL PHARMACOLOGY

n of Action:
mechanism by which topiramate exerts its an-
ilectic is unknown, however, electrophysiological
emical studies of the effects of topiramate on cul-
rons have revealed three properties that may con-
topiramate's antiepileptic efficacy. First, action
ntials elicited repetitively by a sustained depolarization
rons are blocked by topiramate in a time-depen-
ner suggestive of a state-dependent sodium chan-
ing action. Second, topiramate increases the fre-
y of γ-aminobutyrate (GABA) activates $GABA_A$
and enhances the ability of GABA to induce a flux
ions into neurons, suggesting that topiramate
the activity of this inhibitory neurotransmitter.
ity was not blocked by flumazenil, a benzodiazepine
, nor did topiramate increase the duration of the
ant time differentiating topiramate from barbitu-
modulate $GABA_A$ receptors. Third, topiramate
the ability of kainate to activate the kainate/
-amino-3-hydroxy-5-methylisoxazole-4-propionic
(AMPA) subtype of excitatory amino acid (gluta-
ptor, but has no apparent effect on the activity of
D-aspartate (NMDA) at the NMDA receptor sub-
effects of topiramate are concentration-depen-
in the range of 1 μM to 200 μM.
also inhibits some isoenzymes of carbonic anhy-
II and (CA-IV). This pharmacologic effect is gen-
ker than that of acetazolamide, a known carbonic
inhibitor, and is not thought to be a major con-
ibutor to topiramate's antiepileptic activity.
ynamics:
has anticonvulsant activity in rat and mouse
electroshock seizure (MES) tests. Topiramate is
ly effective in blocking clonic seizures induced by
receptor antagonist, pentylenetetrazole.
is also effective in rodent models of epilepsy,
ding tonic and absence-like seizures in the spon-
leptic rat (SER) and tonic and clonic seizures in-
ed by kindling of the amygdala or by global is-

netics:
's formulation is bioequivalent to the immediate
se formulation and, therefore, may be substi-
herapeutic equivalent.
of topiramate is rapid, with peak plasma concen-
curring at approximately 2 hours following a 400
e. The relative bioavailability of topiramate from
rmulation is about 80% compared to a solution.
ilability of topiramate is not affected by food.
okinetics of topiramate are linear with dose
increases in plasma concentration over the
udied (200 to 800 mg/day). The mean plasma
half-life is 21 hours after single or multiple
y state is thus reached in about 4 days in pa-
normal renal function. Topiramate is 13–17%
ean plasma proteins over the concentration
Drug/mL.

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Dose Stabilization	Placebo[a]	Target Topiramate Dosage (mg/day) 200	400	600	800	1,000
YD	N	42	42	40	41	—	—
	Mean Dose	5.9	200	390	556	—	—
	Median Dose	6.0	200	400	600	—	—
YE	N	44	—	—	40	45	40
	Mean Dose	9.7	—	—	544	739	796
	Median Dose	10.0	—	—	600	800	1,000
Y1	N	23	—	19	—	—	—
	Mean Dose	3.8	—	395	—	—	—
	Median Dose	4.0	—	400	—	—	—
Y2	N	30	—	—	28	—	—
	Mean Dose	5.7	—	—	522	—	—
	Median Dose	6.0	—	—	600	—	—
Y3	N	28	—	—	—	25	—
	Mean Dose	7.9	—	—	—	568	—
	Median Dose	8.0	—	—	—	600	—

[a] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocol YD and Y2, 6 tablets/day; Protocol Y3, 8 tablets/day; YE, 10 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy results	Placebo	Target Topiramate Dosage (mg/day) 200	400	600	800	1,000
YD	N	45	45	45	46	—	—
	Mean % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	—	—
	% Responders	18	24	44[d]	46[d]	—	—
YE	N	47	—	—	48	48	47
	Median % Reduction	1.7	—	—	40.8[c]	41.0[c]	36.0[c]
	% Responders	9	—	—	40[c]	41[c]	36[d]
Y1	N	24	—	23	—	—	—
	Median % Reduction	1.1	—	40.7[c]	—	—	—
	% Responders	8	—	35[d]	—	—	—
Y2	N	30	—	—	30	—	—
	Median % Reduction	-12.2	—	—	46.4[c]	—	—
	% Responders	10	—	—	47[c]	—	—
Y3	N	28	—	—	—	28	—
	Median % Reduction	-20.6	—	—	—	24.3[c]	—
	% Responders	0	—	—	—	43[c]	—

Comparisons with placebo; [a]$p = 0.080$; [b]$p \leq 0.010$; [c]$p \leq 0.001$; [d]$p \leq 0.050$; [e]$p = 0.065$; [f]$p \leq 0.005$.

lation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Pharmacokinetic Interaction (see also Drug Interactions):
Antiepileptic Drugs
Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized under **PRECAUTIONS (Table 3).**

Special Populations:
Renal Impairment:
The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30–69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual dose is recommended in patients with moderate or severe renal impairment.

Hemodialysis:
Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20–30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may

Age, Gender, and Race:
Clearance of topiramate was not affected by age (18–67 years), gender, or race.

Pediatric Pharmacokinetics:
Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose. Although the relationship between age and clearance among patients of pediatric age has not been systematically evaluated, it appears that the weight adjusted clearance of topiramate is 50% higher in pediatric patients than in adults.

CLINICAL STUDIES

The studies described in the following section were conducted using TOPAMAX® (topiramate) Tablets.
The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and three comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.
Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8–12 week baseline phase. Patients who experienced at least 12 (or 8, for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® Tablets in addition to their other AEDs. Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or 12-week stabilization period. The numbers of patients ran-

Topamax—Cont.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2.

[See table 2 on previous page]

Subset analyses of the antiepileptic efficacy of TOPAMAX® Tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate capsules) Sprinkle Capsules are contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

Withdrawal of AEDs

Antiepileptic drugs, including TOPAMAX®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Cognitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX® were central nervous system-related. The most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials (see **ADVERSE REACTIONS, Table 5**).

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at dosages above 400 mg/day.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate) Tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).

This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX® (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX® program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS

General:

Kidney Stones

A total of 32/2,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2–4 times that expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see **DOSAGE AND ADMINISTRATION**).

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation (see **PRECAUTIONS: General,** for support regarding hydration as a preventative measure).

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Please refer to the end of the product labeling for important information on how to take TOPAMAX® (topiramate capsules) Sprinkle Capsules.

Drug Interactions:

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

[a] = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

[b] = Is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In a pharmacokinetic interaction study with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX® did not significantly affect the clearance of norethindrone. The mean oral clearance of ethinyl estradiol at 800 mg/day dose was increased by 47% (range: 13–107%). The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a

lymphoma assay; it did not increase unscheduled
thesis in rat hepatocytes *in vitro*; and it did
chromosomal aberrations in human lymphocytes
in rat bone marrow *in vivo*.

No adverse effects on male or female fertility were
in rats at doses up to 100 mg/kg (2.5 times the
mg/m^2 basis).

Pregnancy: Pregnancy Category C.

Topiramate has demonstrated selective developm
icity, including teratogenicity, in experimental a
ies. When oral doses of 20, 100, or 500 mg/kg we
istered to pregnant mice during the period of organ
the incidence of fetal malformations (primarily cra
defects) was increased at all doses. The low dose is
imately 0.2 times the recommended human dose (RHD
mg/day) on a mg/m^2 basis. Fetal body weights and
ossification were reduced at 500 mg/kg in conjunc
decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg
2.5, 30 and 400 mg/kg), the frequency of limb malfor
(ectrodactyly, micromelia, and amelia) was increased
the offspring of dams treated with 400 mg/kg (10 time
RHD on a mg/m^2 basis) or greater during the organo
period of pregnancy. Embryotoxicity (reduced fetal
weights, increased incidence of structural variation
observed at doses as low as 20 mg/kg (0.5 times the RHD
a mg/m^2 basis). Clinical signs of maternal toxicity were
at 400 mg/kg and above, and maternal body weight
was reduced during treatment with 100 mg/kg or greate

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and
mg/kg orally during organogenesis), embryo/fetal mort
was increased at 35 mg/kg (2 times the RHD on a mg/
basis) or greater, and teratogenic effects (primarily rib
vertebral malformations) were observed at 120 mg/kg
times the RHD on a mg/m^2 basis). Evidence of maternal
icity (decreased body weight gain, clinical signs, and/or
tality) was seen at 35 mg/kg and above. When females
were treated during the latter part of gestation
throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20
200 mg/kg), offspring exhibited decreased viability and
layed physical development at 200 mg/kg (5 times the RHD
on a mg/m^2 basis) and reductions in pre- and/or post
ing body weight gain at 2 mg/kg (0.05 times the RHD
mg/m^2 basis) and above.

Maternal toxicity (decreased body weight gain, clini
signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postn
component (0.2, 2.5, 30 or 400 mg/kg during organogen
noted above), pups exhibited delayed physical develop
at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and p
sistent reductions in body weight gain at 30 mg/kg (1 tim
the RHD on a mg/m^2 basis) and higher.

There are no studies using TOPAMAX® in pregna
women. TOPAMAX® should be used during pregnancy o
if the potential benefit outweighs the potential risk to
fetus.

In post-marketing experience, cases of hypospadias h
been reported in male infants exposed in utero to topi
mate, with or without other anticonvulsants; however,
causal relationship with topiramate has not been esta
lished.

Labor and Delivery:

In studies of rats where dams were allowed to deliver pup
naturally, no drug-related effects on gestation length or pa
turition were observed at dosage levels up to 200 mg/kg/day
The effect of TOPAMAX® on labor and delivery in humans
is unknown.

Nursing Mothers:

Topiramate is excreted in the milk of lactating rats. It is no
known if topiramate is excreted in human milk. Since many
drugs are excreted in human milk, and because the poten
tial for serious adverse reactions in nursing infants to
TOPAMAX® is unknown, the potential benefit to the
mother should be weighed against the potential risk to the
infant when considering recommendations regarding nurs
ing.

Pediatric Use:

Safety and effectiveness in children have not been estab
lished. The pharmacokinetic profile of TOPAMAX® was
studied in patients between the ages of 4 and 17 years. (See
**CLINICAL PHARMACOLOGY; Pediatric Pharmacokinet
ics**).

Geriatric Use:

In clinical trials, 2% of patients were over 60. No age relat
difference in effectiveness or adverse effects were seen
There were no pharmacokinetic differences related to a
alone, although the possibility of age-associated renal fa
tional abnormalities should be considered.

Race and Gender Effects:

Evaluation of efficacy and safety in clinical trials has sh
no race or gender related effects.

ADVERSE REACTIONS

The data described in the following section were obtain
using TOPAMAX® (topiramate) Tablets.

The most commonly observed adverse events associa
with the use of topiramate at dosages of 200 to 400 m
in controlled trials, that were seen at greater frequency
topiramate-treated patients and did not appear to be d
related were: somnolence, dizziness, ataxia, speech
ders and related speech problems, psychomotor slo

...oblems, anxiety, mood problems, cognitive prob... ...otherwise specified, weight decreased, and tremor ...5).

...ded clinical trials, 11% of patients receiving topi... ...200 to 400 mg/day as adjunctive therapy discontin... ...to adverse events. This rate appeared to increase at ...above 400 mg/day. Adverse events associated with ...uring therapy included somnolence, dizziness, anxi... ...ulty with concentration or attention, fatigue, and ...esia and increased at dosages above 400 mg/day.

...ately 28% of the 1,715 indiviuals with epilepsy ...ived topiramate at dosages of 200 to 1,600 mg/day ...l studies discontinued treatment because of ad... ...vents; an individual patient could have reported ...than one adverse event.

...dverse events were: psychomotor slowing (4.1%), dif... ...with memory (3.3%), fatigue (3.3%), confusion (3.2%), ...ence (3.2%), difficulty with concentration/attention ...anorexia (2.9%), depression (2.6%), dizziness (2.6%), ...decrease (2.5%), nervousness (2.2%), ataxia (2.2%), ...thesia (2.0%), and language problems (2.0%).

...s in Controlled Clinical Trials—Add-On Therapy

...lists treatment-emergent adverse events that oc... ...at least 1% of patients treated with 200 to 400 ...topiramate in controlled trials that were numeri... ...more common at this dose than in the patients treated ...placebo. In general, most patients who experienced ad... ...events during the first eight weeks of these trials no ...experienced them by their last visit.

...scriber should be aware that these data were ob... ...when TOPAMAX® was added to concurrent antiepi... ...drug therapy and cannot be used to predict the fre... ...of adverse events in the course of usual medical ...ce where patient characteristics and other factors may ...from those prevailing during clinical studies. Simi... ...the cited frequencies cannot be directly compared with ...obtained from other clinical investigations involving ...treatments, uses, or investigators. Inspection of ...frequencies, however, does provide the prescribing ...ian with a basis to estimate the relative contribution ...g and non-drug factors to the adverse event incidences ...population studied.

...table 4 above]

...table 5 at top of next page]

...Adverse Events Observed

...events that occurred in more than 1% of patients ...with 200 to 400 mg of topiramate in placebo-con... ...trials but with equal or greater frequency in the pla... ...group were: fatigue, headache, injury, anxiety, rash, ...convulsions aggravated, coughing, gastroenteritis, rhi... ...back pain, hot flushes, bronchitis, abnormal gait, in... ...untary muscle contractions, and epistaxis.

...Adverse Events Observed During All Clinical Trials

...ramate, initiated as adjunctive therapy, has been ad... ...ered to 1,715 patients with epilepsy during all clinical ...During these studies, all adverse events were re... ...by the clinical investigators using terminology of ...own choosing. To provide a meaningful estimate of the ...portion of individuals having adverse events, similar ...of events were grouped into a smaller number of stan... ...ized categories using modified WHOART dictionary ...nology. The frequencies presented represent the pro... ...of 1,715 topiramate-treated patients who experi... ...an event of the type cited on at least one occasion ...receiving topiramate. Reported events are included ...those already listed in the previous table, those too ...to be informative, and those not reasonably associ... ...with the use of the drug.

...are classified within body system categories and ...erated in order of decreasing frequency using the fol... ...definitions: *frequent* occurring in at least 1/100 pa... ...*infrequent* occurring in 1/100 to 1/1000 patients; *rare* ...ing in fewer than 1/1000 patients.

...mic **Nervous System Disorders:** *Infrequent:* vaso...

...s **Whole:** *Frequent:* fatigue, fever, malaise. *Infre...* ...syncope, halitosis, abdomen enlarged. *Rare:* alcohol ...nce, substernal chest pain, sudden death.

...vascular Disorders, General:** *Infrequent:* hyperten... ...hypotension, postural hypotension.

...& **Peripheral Nervous System Disorders:** *Fre...* ...hypokinesia, vertigo, stupor, convulsions grand mal, ...nesia, hypertonia. *Infrequent:* leg cramps, hypore... ...neuropathy, migraine, apraxia, hyperaesthesia, dys... ...hyperreflexia, dysphonia, scotoma, ptosis, dystonia, ...field defect, coma, encephalopathy, fecal incont... ...upper motor neuron lesion. *Rare:* cerebellar syn... ...EEG abnormal, tongue paralysis.

...ne Disorders:** *Infrequent:* goiter. *Rare:* thyroid dis...

...estinal System Disorders:** *Frequent:* diarrhea, ...flatulence, gastroenteritis. *Infrequent:* gum hyper... ...hemorrhoids, tooth caries, stomatitis, dysphagia, ...gastritis, saliva increased, hiccough, gastroesopha... ...tongue edema, esophagitis. *Rare:* eructation.

...and Vestibular Disorders:** *Frequent:* tinnitus. ...ache, hyperacusis.

...and Rhythm Disorders:** *Frequent:* palpitation. ...AV block, bradycardia, bundle branch block. ...rhythmia, arrhythmia atrial, fibrillation atrial.

...tary System Disorders:** *Infrequent:* SGPT in...

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials[a,b]
(Events that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event[c]	TOPAMAX® Dosage (mg/day) Placebo (N=174)	200–400 (N=113)	600–1,000 (N=247)
Body as a Whole - General Disorders			
Asthenia	1.1	8.0	4.5
Back Pain	4.0	6.2	2.0
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	3.2
Leg Pain	2.3	3.5	2.4
Hot Flushes	1.7	2.7	0.8
Body Odor	0.0	1.8	0.0
Edema	1.1	1.8	1.2
Rigors	0.0	1.8	0.4
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.4
Ataxia	6.9	21.2	17.0
Speech Disorders/ Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.6
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoaesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female	(N=39)	(N=24)	(N=42)
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.5
Eye Pain	1.1	1.8	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

Topamax—Cont.

tase increased, dehydration, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, creatinine increased, hyperchloremia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypocholesterolemia, hypoglycemia, hypophosphatemia.

Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.

Myo-, Endo-, Pericardial & Valve Disorders: *Infrequent:* angina pectoris.

Neoplasms: *Infrequent:* basal cell carcinoma, thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, purpura, thrombocytopenia, pulmonary embolism.

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngismus.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhoea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Frequent:* taste perversion. *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdosage is not recommended. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve responses.

The recommended total daily dose of TOPAMAX® (topiramate capsules) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®.

Table 5: Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	Placebo (N=174)	TOPAMAX® Dosage (mg/day) 200 (N=45)	400 (N=68)	600-1 (N=2
Fatigue	14.4	11.1	11.8	30
Nervousness	7.5	13.3	17.6	20
Difficulty with Concentration/Attention	1.1	6.7	8.8	15
Confusion	5.2	8.9	10.3	15
Depression	6.3	8.9	7.4	13
Anorexia	4.0	4.4	5.9	11
Language problems	0.6	2.2	8.8	11
Anxiety	5.2	2.2	2.9	9
Mood problems	1.7	0.0	5.9	10
Cognitive problems NOS	0.6	0.0	0.0	4
Weight decrease	2.3	4.4	8.8	12
Tremor	6.3	13.3	8.8	13

small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an antiseizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off-white spheres. The gelatin capsules are white and clear.

They are marked as follows:

15 mg capsules with "TOP" and "15 mg" on the side.

25 mg capsules with "TOP" and "25 mg" on the side.

The capsules are supplied as follows:

15 mg capsules bottles of 60 (NDC 0045-0647-65)

25 mg capsules bottles of 60 (NDC 0045-0645-65)

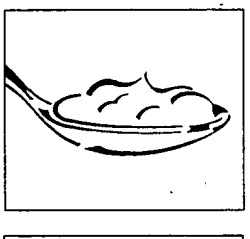
TOPAMAX® (topiramate capsules) Sprinkle Capsules should be stored in tightly-closed containers at or below 25° C (77°F). Protect from moisture.

TOPAMAX® (topiramate capsules) is a trademark of OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC.

HOW TO TAKE TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES

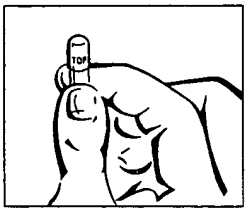
A Guide for Patients and Their Caregivers

Your doctor has given you a prescription for TOPAMAX® (topiramate capsules) Sprinkle Capsules. Here are your instructions for taking this medication. Please read these instructions prior to use.

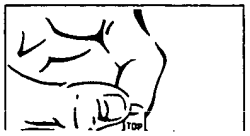


To Take With Food

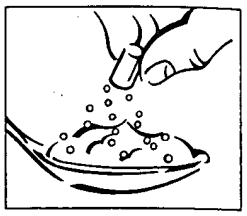
You may sprinkle the contents of TOPAMAX® Sprinkle Capsules on a small amount (teaspoon) of soft food, such as applesauce, custard, ice cream, oatmeal, pudding, or yogurt.



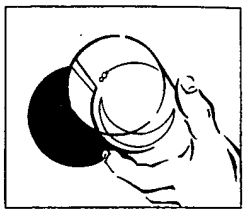
Hold the capsule upright so that you can read the word "TOP".



Carefully twist off the clear portion of the capsule. You may find it best to do this over the small portion of the food onto which you will be pouring the



Sprinkle all of the sule's contents spoonful taking care to the entire dosage onto the food.



Be sure swallows spoonful kle/food diately. should be avoided may be helpful to the patient/drink immediately make sure mixture IMPORTANT store any mixture later time.

To Take Without Food

TOPAMAX® Sprinkle Capsules may also be swallowed whole capsules.

For more information about TOPAMAX® Sprinkle Capsules, ask your doctor or pharmacist.

OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, NJ 08869
© OMP 1998 Issued February 1999 643-10-45

Shown in Product Identification Guide, page 422

TOPAMAX®

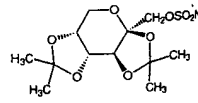
[tō'-pă-măx]

(topiramate) tablets

DESCRIPTION

TOPAMAX® (topiramate) is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic drug. It is available as 25 mg, 100 mg, and 200 mg round tablets for oral administration.

Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.36. Topiramate is designated chemically as 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX® (topiramate) Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide (100 and 200 mg tablets), and polysorbate 80.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The precise mechanism by which topiramate exerts its antiseizure effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on cultured neurons have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, it

enhances the ability of GABA to induce a flux ions into neurons, suggesting that topiramate the activity of this inhibitory neurotransmitter. was not blocked by flumazenil, a benzodiazepine ator, did topiramate increase the duration of the n time, differentiating topiramate from barbitu- modulate $GABA_A$ receptors. Third, topiramate the ability of kainate to activate the kainate/ mino-3-hydroxy-5-methylisoxazole-4-propionic NMDA) subtype of excitatory amino acid (gluta- e, but has no apparent effect on the activity of p-aspartate (NMDA) at the NMDA receptor sub- effects of topiramate are concentration-depen- the range of 1 µM to 200 µM.

also inhibits some isoenzymes of carbonic anhy- B and CA-IV). This pharmacologic effect is gen- r than that of acetazolamide, a known carbonic inhibitor, and is not thought to be a major con- utor to topiramate's antiepileptic activity.

ynamics:

has anticonvulsant activity in rat and mouse electroshock-seizure (MES) tests. Topiramate is effective in blocking clonic seizures induced by receptor antagonist, pentylenetetrazole. Topira- effective in rodent models of epilepsy, which in- and absence-like seizures in the spontaneous ep- SER) and tonic and clonic seizures induced in dling of the amygdala or by global ischemia.

kinetics:

Topiramate is rapid, with peak plasma concen- urring at approximately 2 hours following a 400 . The relative bioavailability of topiramate from rmulation is about 80% compared to a solution. ability of topiramate is not affected by food. e pharmacokinetics of topiramate are linear with dose ll increases in plasma concentration over the studied (200 to 800 mg/day). The mean plasma half-life is 21 hours after single or multiple dy state is thus reached in about 4 days in pa- normal renal function. Topiramate is 13–17% human plasma proteins over the concentration 250 µg/mL.

n and Excretion:

is not extensively metabolized and is primarily unchanged in the urine (approximately 70% of ered dose). Six metabolites have been identified none of which constitutes more than 5% of an ed dose. The metabolites are formed via hydrox- olysis, and glucuronidation. There is evidence ular reabsorption of topiramate. In rats, given o inhibit tubular reabsorption, along with topi- gnificant increase in renal clearance of topira- served. This interaction has not been evaluated Overall, plasma clearance is approximately 20 in humans following oral administration.

kinetic Interactions (see also Drug Interactions):

Drugs

interactions between topiramate and standard assessed in controlled clinical pharmacokinetic atients with epilepsy. The effect of these inter- can plasma AUCs are summarized under PRE- (Table 3).

ulations:

ment:

ce of topiramate was reduced by 42% in moder- impaired (creatinine clearance 30–69 mL/min/ by 54% in severely renally impaired subjects earance <30 mL/min/1.73m²) compared to nor- ction subjects (creatinine clearance >70 mL/). Since topiramate is presumed to undergo sig- ular reabsorption, it is uncertain whether this can be generalized to all situations of renal im- It is conceivable that some forms of renal disease ntially affect glomerular filtration rate and tub- ction resulting in a clearance of topiramate not creatinine clearance. In general, however, use the usual dose is recommended in patients with severe renal impairment.

is cleared by hemodialysis. Using a high effi- flow, single pass-dialysate hemodialysis pro- piramate dialysis clearance was 120 mL/min with hrough the dialyzer at 400 mL/min. This high compared to 20–30 mL/min total oral clearance ubilite) will remove a clinically significant piramate from the patient over the hemodialy- d period. Therefore, a dose adjustment may be (DOSAGE AND ADMINISTRATION).

ment:

ly impaired subjects, the clearance of topira- decreased; the mechanism underlying the de- well understood.

and Race:

topiramate was not affected by age (18–67 , or race.

macokinetics:

tics of topiramate were evaluated in patients ars) receiving one or two other antiepileptic kinetic profiles were obtained after one 0, 5 and 9 mg/kg/day. Clearance was inde-

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

			Target Topiramate Dosage (mg/day)				
Protocol	Stabilization Dose	Placebo[a]	200	400	600	800	1,000
YD	N	42	42	40	41	-	-
	Mean Dose	5.9	200	390	556	-	-
	Median Dose	6.0	200	400	600	-	-
YE	N	44	-	-	40	45	40
	Mean Dose	9.7	-	-	544	739	796
	Median Dose	10.0	-	-	600	800	1,000
Y1	N	23	-	19	-	-	-
	Mean Dose	3.8	-	395	-	-	-
	Median Dose	4.0	-	400	-	-	-
Y2	N	30	-	-	28	-	-
	Mean Dose	5.7	-	-	522	-	-
	Median Dose	6.0	-	-	600	-	-
Y3	N	28	-	-	-	25	-
	Mean Dose	7.9	-	-	-	568	-
	Median Dose	8.0	-	-	-	600	-

[a]Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocol Y3, 8 tablets/day; Protocols YE, 10 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

			Target Topiramate Dosage (mg/day)				
Protocol	Efficacy Results	Placebo	200	400	600	800	1,000
YD	N	45	45	45	46	-	-
	Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	-	-
	% Responders	18	24	44[d]	46[d]	-	-
YE	N	47	-	-	48	48	47
	Median % Reduction	1.7	-	-	40.8[c]	41.0[c]	36.0[c]
	% Responders	9	-	-	40[c]	41[c]	36[d]
Y1	N	24	23				
	Median % Reduction	1.1	40.7[e]				
	% Responders	8	35[d]				
Y2	N	30	-	-	30	-	-
	Median % Reduction	12.2	-	-	46.4[f]	-	-
	% Responders	10	-	-	47	-	-
Y3	N	28	-	-	-	28	-
	Median % Reduction	20.6	-	-	-	24.3[c]	-
	% Responders	0	-	-	-	43[d]	-

Comparisons with placebo: [a]p = 0.080, [b] p≤0.010; [c] p≤0.001; [d] p≤0.050; [e]p=0.065; [f] p≤0.005

CLINICAL STUDIES

The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and three comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8–12 week baseline phase. Patients who experienced at least 12 (or 8, for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or 12-week stabilization period. The numbers of patients randomized to each dose, and the actual mean, and median doses in the stabilization period are shown in Table 1.

[See table 1 above]

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2.

[See table 2 above]

Subset analyses of the antiepileptic efficacy of TOPAMAX® in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate) is indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate) is contraindicated in patients with a history of hypersensitivity to any component of this product.

Cognitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX® were central nervous system-related. The most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials [see **ADVERSE REACTIONS, Table 5**].

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at dosages above 400 mg/day.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate), 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).

This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS

General:

Kidney Stones

A total of 32/2,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2–4 times that expected in a sim-

Topamax—Cont.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see **DOSAGE AND ADMINISTRATION**).

Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation [see **PRECAUTIONS: General**, for support regarding hydration as a preventative measure].

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Drug Interactions:

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

[a] = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

[b] = is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX® did not significantly affect the clearance of norethindrone. The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials[a,b] (Events that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event[c]	TOPAMAX® Dosage (mg/day) Placebo (N=174)	200-400 (N=113)	600-1,000 (N=247)
Body as a Whole - General Disorders			
Asthenia	1.1	8.0	
Back Pain	4.0	6.2	4.5
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	2.0
Leg Pain	2.3	3.5	3.2
Hot Flushes	1.7	2.7	2.4
Body Odor	0.0	1.8	0.8
Edema	1.1	1.8	0.0
Rigors	0.0	1.8	1.2
			0.4
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	
Ataxia	6.9	21.2	32.4
Speech Disorders/ Related Speech Problems	2.9	16.8	17.0
			13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.6
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoaesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female	(N=39)	(N=24)	(N=42)
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.5
Eye Pain	1.1	1.8	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.

[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[c] Adverse events reported by at least 1% of patients in the TOPAMAX 200-400 mg/day group and more common than in the placebo group are listed in this table.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300

sures measured in patients receiving topiramate therapy at the recommended human dose (RHD) of 400 and 1.5 to 2 times steady state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2

mutagenic in the Ames test or the *in vitro* mouse ma assay; it did not increase unscheduled DNA syn- in rat hepatocytes *in vitro*; and it did not increase somal aberrations in human lymphocytes *in vitro* or bone marrow *in vivo*.

verse effects on male or female fertility were observed s at doses up to 100 mg/kg (2.5 times the RHD on a basis).

gory: Pregnancy Category C.

mate has demonstrated selective developmental tox- including teratogenicity, in experimental animal stud- When oral doses of 20, 100, or 500 mg/kg were admin- ed to pregnant mice during the period of organogenesis, idence of fetal malformations (primarily craniofacial cts) was increased at all doses. The low dose is approx- ely 0.2 times the recommended human dose (RHD=400 g/m^2 basis. Fetal body weights and skeletal ation were reduced at 500 mg/kg in conjunction with reased maternal body weight gain.

rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, 1.0 and 400 mg/kg), the frequency of limb malformations dactyly, micromelia, and amelia) was increased among spring of dams treated with 400 mg/kg (10 times the RHD on a mg/m^2 basis) or greater during the organogenesis od of pregnancy. Embryotoxicity (reduced fetal body ghts, increased incidence of structural variations) was erved at doses as low as 20 mg/kg (0.5 times the RHD on g/m^2 basis). Clinical signs of maternal toxicity were seen 00 mg/kg and above, and maternal body weight gain reduced during treatment with 100 mg/kg or greater.

rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 g/kg orally during organogenesis), embryo/fetal mortality s increased at 35 mg/kg (2 times the RHD on a mg/m^2 s) or greater, and teratogenic effects (primarily rib and ebral malformations) were observed at 120 mg/kg (6 s the RHD on a mg/m^2 basis). Evidence of maternal tox- decreased body weight gain, clinical signs, and/or mor- ity) was seen at 35 mg/kg and above.

female rats were treated during the latter part of ges- on and throughout lactation (0.2, 4, 20, and 100 mg/kg or 0 and 200 mg/kg), offspring exhibited decreased viabil- and delayed physical development at 200 mg/kg (5 times RHD on a mg/m^2 basis) and reductions in pre- and/or weaning body weight gain at 2 mg/kg (0.05 times the HD on a mg/m^2 basis) and above. Maternal toxicity (de- ed body weight gain, clinical signs) was evident at 100 g/kg or greater.

rat embryo/fetal development study with a postnatal mponent (0.2, 2.5, 30 or 400 mg/kg during organogenesis; ed above), pups exhibited delayed physical development 400 mg/kg (10 times the RHD on a mg/m^2 basis) and per- ent reductions in body weight gain at 30 mg/kg (1 times RHD on a mg/m^2 basis) and higher.

re are no studies using TOPAMAX® (topiramate) in gnant women. TOPAMAX® should be used during preg- only if the potential benefit outweighs the potential to the fetus.

ost-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topira- with or without other anticonvulsants; however, a l relationship with topiramate has not been estab-

or and Delivery:

dies of rats where dams were allowed to deliver pups ally, no drug-related effects on gestation length or par- on were observed at dosage levels up to 200 mg/kg/day. effect of TOPAMAX® (topiramate) on labor and delivery humans is unknown.

g Mothers:

amate is excreted in the milk of lactating rats. It is not if topiramate is excreted in human milk. Since many are excreted in human milk, and because the poten- serious adverse reactions in nursing infants to AMAX® (topiramate) is unknown, the potential benefit mother should be weighed against the potential risk infant when considering recommendations regarding

e Use:

and effectiveness in children have not been estab- The pharmacokinetic profile of TOPAMAX® was n patients between the ages of 4 and 17 years [see CAL PHARMACOLOGY; Pediatric Pharmacokinet-

e Use:

l trials, 2% of patients were over 60. No age related ce in effectiveness or adverse effects were seen. were no pharmacokinetic differences related to age although the possibility of age-associated renal func- normalities should be considered.

and Gender Effects:

sis of efficacy and safety in clinical trials has shown gender related effects.

REACTIONS

commonly observed adverse events associated se of topiramate at dosages of 200 to 400 mg/day olled trials, that were seen at greater frequency in reated patients and did not appear to be dose- somnolence, dizziness, ataxia, speech disor- related speech problems, psychomotor slowing, and paresthesia [see Table 4]. The most com- lled adverse events at dosages of 200 to 1,000 fatigue, nervousness, difficulty with concen-

Table 5: Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	Placebo (N=174)	TOPAMAX® Dosage (mg/day) 200 (N=45)	400 (N=68)	600-1,000 (N=247)
Fatigue	14.4	11.1	11.8	30.8
Nervousness	7.5	13.3	17.6	20.6
Difficulty with Concentration/Attention	1.1	6.7	8.8	15.4
Confusion	5.2	8.9	10.3	15.0
Depression	6.3	8.9	7.4	13.4
Anorexia	4.0	4.4	5.9	11.3
Language problems	0.6	2.2	8.8	11.7
Anxiety	5.2	2.2	2.9	9.3
Mood problems	1.7	0.0	5.9	10.1
Cognitive problems NOS	0.6	0.0	0.0	4.0
Weight decrease	2.3	4.4	8.8	12.6
Tremor	6.3	13.3	8.8	13.8

guage problems, anxiety, mood problems, cognitive problems not otherwise specified, weight decreased, and tremor [see Table 5].

In controlled clinical trials, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued due to adverse events. This rate appeared to increase at dosages above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day.

Approximately 28% of the 1,715 individuals with epilepsy who received topiramate at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event. These adverse events were: psychomotor slowing (4.1%), difficulty with memory (3.3%), fatigue (3.3%), confusion (3.2%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.9%), depression (2.6%), dizziness (2.6%), weight decrease (2.5%), nervousness (2.2%), ataxia (2.2%), paresthesia (2.0%), and language problems (2.0%).

Incidence in Controlled Clinical Trials – Add-On Therapy

Table 4 lists treatment-emergent adverse events that occurred in at least 1% of patients treated with 200 to 400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse events during the first eight weeks of these trials no longer experienced them by their last visit.

The prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does not provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

[See table 4 at top of previous page]

[See table 5 above]

Other Adverse Events Observed

Other events that occurred in more than 1% of patients treated with 200 to 400 mg of topiramate in placebo-controlled trials but with equal or greater frequency in the placebo group were: fatigue, headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, gastroenteritis, rhinitis, back pain, hot flushes, bronchitis, abnormal gait, involuntary muscle contractions, and epistaxis.

Other Adverse Events Observed During All Clinical Trials

Topiramate, initiated as adjunctive therapy, has been administered to 1,715 patients with epilepsy during all clinical studies. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of 1,715 topiramate-treated patients who experienced an event of the type cited on at least one occasion while receiving topiramate. Reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients; *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

Body as a Whole: *Frequent:* fatigue, fever, malaise. *Infrequent:* syncope, halitosis, abdomen enlarged. *Rare:* alcohol intolerance, substemal chest pain, sudden death.

Cardiovascular Disorders, General: *Infrequent:* hypertension, hypotension, postural hypotension.

Central & Peripheral Nervous System Disorders: *Frequent:* hypokinesia, vertigo, stupor, convulsions grand mal, hyperkinesea, hypertonia. *Infrequent:* leg cramps, hyporeflexia, neuropathy, migraine, ataxia, hyperaesthesia, dyskinesia, field defect, coma, encephalopathy, fecal incontinence, upper motor neuron lesion. *Rare:* cerebellar syndrome, EEG abnormal, tongue paralysis.

Endocrine Disorders: *Infrequent:* goiter. *Rare:* thyroid disorder.

Gastrointestinal System Disorders: *Frequent:* diarrhea, vomiting, flatulence, gastroenteritis. *Infrequent:* gum hyperplasia, hemorrhoids, tooth caries, stomatitis, dysphagia, melena, gastritis, saliva increased, hiccough, gastroesophageal reflux, tongue edema, esophagitis. *Rare:* eructation.

Hearing and Vestibular Disorders: *Frequent:* tinnitus. *Rare:* earache, hyperacusis.

Heart Rate and Rhythm Disorders: *Frequent:* palpitation. *Infrequent:* AV block bradycardia, bundle branch block. *Rare:* arrhythmia, arrhythmia atrial, fibrillation atrial.

Liver and Biliary System Disorders: *Infrequent:* SGPT increased, SGOT increased, gall bladder disorder. *Rare:* gamma-GT increased.

Metabolic and Nutritional Disorders: *Frequent:* weight increase. *Infrequent:* thirst, hypokalemia, alkaline phosphatase increased, dehydration, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, creatinine increased, hyperchloremia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypocholesterolemia, hypoglycemia, hypophosphatemia.

Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.

Myo-, Endo-, Pericardial & Valve Disorders: *Infrequent:* angina pectoris.

Neoplasms: *Infrequent:* basal cell carcinoma, thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, purpura, thrombocytopenia, pulmonary embolism.

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngismus.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhoea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Frequent:* taste perversion. *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® (topiramate) has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdosage is not recommended. Treatment should be ap-

Continued on next page

Topamax—Cont.

propriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve responses.

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®. Because of the bitter taste, tablets should not be broken.

TOPAMAX® can be taken without regard to meals.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an antiseizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate) is available as debossed, coated, round tablets in the following strengths and colors:

25 mg white (coded "TOP" on one side; "25" on the other)

100 mg yellow (coded "TOPAMAX" on one side; "100" on the other)

200 mg salmon (coded "TOPAMAX" on one side; "200" on the other)

They are supplied as follows:

25 mg tablets – bottles of 60 count with desiccant (NDC 0045-0639-65)

100 mg tablets – bottles of 60 count with desiccant (NDC 0045-0641-65)

200 mg tablets – bottles of 60 count with desiccant (NDC 0045-0642-65)

TOPAMAX® (topiramate) Tablets should be stored in tightly-closed containers at controlled room temperature, (59 to 86°F, 15 to 30°C). Protect from moisture.

TOPAMAX® (topiramate) is a trademark of OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC.

Raritan, NJ 08869

 Revised February 1999 643-10-443-5

Shown in Product Identification Guide, page 329

TYLENOL® with Codeine ℞

[ti 'len-awl co 'dēn]

(acetaminophen and codeine phosphate tablets and oral solution USP)

Tablets Ⓒ Ⅲ and Elixir Ⓒ Ⅴ

Analgesic For Oral Use

No. 3-NSN 6505-00-400-2054—100's

No. 3-NSN 6505-00-147-8347—500's

No. 3-NSN 6505-01-086-2993—U/D 500's

No. 3-NSN 6505-00-372-3032—1000's

Elixir-NSN 6505-01-035-1963—Pints

No. 3 Codeine Phosphate*	30 mg
Acetaminophen	300 mg
No. 4 Codeine Phosphate*	60 mg
Acetaminophen	300 mg

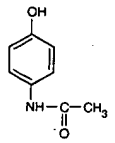
Each 5 mL of elixir contains:

Codeine Phosphate*	12 mg
Acetaminophen	120 mg
Alcohol	7%

**Warning* —May be habit forming.

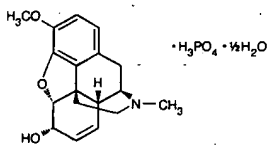
Inactive ingredients: tablets—powdered cellulose, magnesium stearate, sodium metabisulfite†, pregelatinized starch, starch (corn); elixir—alcohol, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, FD&C Yellow No.6.

Acetaminophen, 4 '-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its structure is as follows:



C_8H_9NO M.W. 151.16

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-didehydro- 4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. Its structure is as follows:



$C_{18}H_{21}NO_3.H_3PO_4.\ ^1/_2H_2O$ M.W. 406.37

†See WARNINGS

CLINICAL PHARMACOLOGY

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) combine the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingredients are well absorbed orally. The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen, and from 2.5 to 3 hours for codeine.

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10 percent of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Acetaminophen is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

INDICATIONS AND USAGE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are indicated for the relief of mild to moderately severe pain.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

TYLENOL with Codeine tablets or elixir (acetaminophen and codeine phosphate tablets and oral solution USP) should not be administered to patients who have previously exhibited hypersensitivity to any component.

WARNINGS

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exag-

Acute Abdominal Conditions: The administration of this product or other narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Special Risk Patients: This drug should be given with caution to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Codeine may impair the mental and/or physical ability required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients using this drug should be cautioned accordingly.

The patient should understand the single-dose and 24-hour dose limits, and the time interval between doses.

Drug Interactions

Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with codeine may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the higher doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryonic resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant rats reportedly resulted in delayed ossification in the offspring.

There are no studies in humans, and the significance of these findings to humans, if any, is not known.

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic dosage. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.

Pediatric Use

Safe dosage of TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) has not been established in children below the age of three years.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain and pruritus.

At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are a Schedule III controlled substance.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is a Schedule V controlled substance.

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic

DECLARATION UNDER 37 C.F.R. § 1.132
Examining Group 1614
Patent Application
Docket No. UF-260XC1
Serial No. 09/997,447

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Phyllis G. Spivack
Art Unit	:	1614
Applicants	:	Nathan Andrew Shapira, Mary Catherine Lessig, Daniel John Driscoll
Serial No.	:	09/997,447
Filed	:	November 30, 2001
Conf. No.	:	3440
For	:	Treatments for Neurogenetic Disorders, Impulse Control Disorders, and Wound Healing

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION OF DAVID W. MOZINGO, M.D.. UNDER 37 C.F.R. §1.132

Sir:

I, David W. Mozingo, M.D., hereby declare:

THAT, I have received the following degrees:

Doctor of Medicine	1984	University of Virginia School of Medicine, Charlottesville, Virginia
Bachelor of Science in Chemistry	1980	University of Virginia, Charlottesville, Virginia

THAT, I have been employed professionally as follows:

Postdoctoral Training

1990- 1991	Fellowship, Surgical Critical Care Fellowship, Brooke Army Medical Center, Fort Sam Houston, Texas
1986-1990	Residency, General Surgery Residency, Brooke Army Medical Center, Fort Sam Houston, Texas
1984-1985	Internship, Categorical Surgery Internship, Brooke Army Medical Center, Fort Sam Houston, Texas

Academic Appointments

2002-present	Professor of Surgery and Anesthesiology, University of Florida College of Medicine, Gainesville, Florida
1996 – 2002	Associate Professor of Surgery and Anesthesiology, University of Florida College of Medicine, Gainesville, Florida
1992 – 1996	Clinical Assistant Professor of Surgery, University of Texas Health Science Center, San Antonio, Texas
1993 – 1996	Assistant Professor of Surgery, F. Edward Hebert School of Medicine, Uniformed Services University of Health Science, Bethesda, Maryland
1992 – 1992	Clinical Instructor in Surgery, University of Texas Health Science Center, San Antonio, Texas
1991 – 1996	Faculty, Surgical Critical Care Fellowship, Brooke Army Medical Center, Fort Sam Houston, Texas
1991 – 1996	Faculty, General Surgery Residency Program, Brooke Army Medical Center, Fort Sam Houston, Texas
1990 – 1993	Instructor of Surgery, F. Edward Hebert School of Medicine, Uniformed Services University of Health Science, Bethesda, Maryland

THAT, I have authored approximately sixty research papers, chapters and review articles publications (a sampling of which is included on the attached Curriculum Vitae);

THAT, through my years of research, I have kept up to date on the technical literature and maintained contact with experts in the field by participating in professional meetings and

seminars, and by direct personal contact. As a result, I am familiar with the general level of skill of those working in the field of wound healing;

THAT, I have studied application Serial No. 09/997,447, filed on November 30, 2001, the Office Actions which have been issued during prosecution of this application, the references cited in these Office Actions, and the responses which have been filed on the behalf of Applicants. Thus, being duly qualified, I declare as follows:

1. I have reviewed the disclosure of Blake *et al.* (International Application PCT /GB99/02606; International Publication No. WO 00/10610) and cannot agree with the assertion of the Patent Office that this reference would motivate one skilled in the art to use topiramate to promote wound healing. The reference is directed to the manufacture and use of bioreductive conjugates for the treatment of a variety of conditions or diseases. While the reference addresses or claims medicaments for "use in the healing of wounds or the treatment of fibrotic disorders", the therapeutic agents indicated as being useful in this regard are limited to growth factor neutralizing agents or agents specific against only fibrotic growth factors (see claims 2 and 3); the reference specifically speaks to neutralizing growth factors, interleukins, or other agents that are typically associated with inducing fibrosis or scarring. Specific examples of such agents that are provided in the description of Blake *et al.* are TGF-β1; TGF-β2; PDGF; IFNγ; IL-1; TGF-β3; FGF-1; FGF-2; IL-4; IL-10; betaglycan; inhibitors of: IFN-γ, at least one integrin receptor, at least one convertase enzyme, or IL-6; stimulators of: IFN-γ or activin and/or inhibin; agents that modulate actin assembly and organization, latency associated peptide; insulin like growth factor II; or compounds that influence the sex hormone system (see claims 4-21 and the description of the embodiment directed to wound healing at pages 4-14). Indeed, the description at pages 4-14 repeatedly states that the embodiments discussed on these pages are directed to wound healing (see, for example, page 7, paragraph 5; page 8, paragraphs 1 and 4; page 9, paragraphs 2 and 6; page 10, paragraph 2; page 11, paragraphs 3 and 7; page 12, paragraphs 2 and 5; page 13, paragraph 4; and page 14, paragraphs 1 and 4).

I note that topiramate is absent from the listing of agents for use in promoting the healing of wounds or the treatment of fibrotic disorders. This is not surprising as, to the best of my knowledge, there was no recognition (nor was it suspected) that topiramate had such an activity prior to the filing date of this patent application. As the Patent Office may be aware, topiramate is a drug recommended for the treatment of epilepsy (as is disclosed in the description of Blake *et al.* at page 15, paragraph 1 and the Physician's Desk Reference, a copy of which is appended hereto).

As one skilled in the art, I would not have been motivated to use topiramate for the treatment of wounds or for promoting wound healing in view of the teachings of Blake *et al.* Rather, I would have been motivated to use topiramate for the treatment of epilepsy. Furthermore, as one skilled in the art, I would not, and could not, reasonably infer that the reference teaches or suggests or motivates the use of topiramate for promoting wound healing as is argued by the Patent Office.

2. As indicated above, there was, to the best of my knowledge, no recognition in the art that topiramate was useful for promoting wound healing in individuals to whom topiramate was administered and, based upon my experience in the field, I would not have expected topiramate to provide therapeutic benefit in promoting wound healing.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Further declarant sayeth naught.

Signed: _____ Date: 9/22/04
David W. Mozingo, M.D.

Attachments: Physician's Desk Reference (2000)

CURRICULUM VITAE

David W. Mozingo, MD, FACS

October 6, 2004

PERSONAL INFORMATION

Citizenship	United States
Business Address	University of Florida Department of Surgery PO Box 100286 Gainesville, FL 32610-0286
Business Telephone	352-265-0262
Business Fax	352-338-9809

EDUCATION

Undergraduate	University of Virginia, Charlottesville, Virginia Bachelor of Science in Chemistry May 1980
Medical School	University of Virginia School of Medicine Charlottesville, Virginia, Doctor of Medicine May 1984

POSTGRADUATE TRAINING

Fellowship	Surgical Critical Care Fellowship, Brooke Army Medical Center, Fort Sam Houston, Texas, July 1990-June 1991
Residency	General Surgery Residency, Brooke Army Medical Center, Fort Sam Houston, Texas, July 1986-June 1990
Internship	Categorical Surgery Internship, Brooke Army Medical Center, Fort Sam Houston, Texas, July 1984-June 1985

AWARDS

American Burn Association Traveling Fellowship, April 1992
General Surgery Resident Research Award, Brooke Army Medical Center, June 1988
University of Virginia – Graduation with Distinction, May 1980
University of Virginia – Intermediate Honors, 1978
Meritorious Service Medal
US Army Superior Unit Award

National Defense Service Medal
Air Crew Member Badge
Army Service Ribbon

PROFESSIONAL LICENSES & BOARD CERTIFICATIONS

1986-Present License – Commonwealth of Virginia #0101040452 10/31/86
1996-Present License – State of Florida #ME0070020 2/26/96

American Board of Surgery, 2/28/91, Re-certification 1999
American Board of Surgery, Certificate of Added Qualifications in Surgical Critical Care, 10/18/91, Re-certification 2000
National Board of Medical Examiners, April 1986
American College of Surgeons – Advance Trauma Life Support – Provider, April 1985
American College of Surgeons – Advanced Trauma Life Support – Instructor, March 1990, Re-certification March 1994
American Heart Association – Advanced Cardiac Life Support – Provider, March 1996
American Burn Association – Advanced Burn Life Support – Instructor/Provider, February 1994; National Faculty, 1995

ACADEMIC APPOINTMENTS

2002 – present Professor of Surgery and Anesthesiology
University of Florida College of Medicine
Gainesville, Florida

1996 – 2002 Associate Professor of Surgery and Anesthesiology
University of Florida College of Medicine
Gainesville, Florida

1992 – 1996 Clinical Assistant Professor of Surgery
University of Texas Health Science Center
San Antonio, Texas

1993 – 1996 Assistant Professor of Surgery
F. Edward Hebert School of Medicine
Uniformed Services University of Health Science
Bethesda, Maryland

1992 – 1992 Clinical Instructor in Surgery
University of Texas Health Science Center
San Antonio, Texas

1991 – 1996 Faculty, Surgical Critical Care Fellowship
Brooke Army Medical Center
Fort Sam Houston, Texas

1991 – 1996 Faculty, General Surgery Residency Program
Brooke Army Medical Center
Fort Sam Houston, Texas

1990 – 1993	Instructor of Surgery F. Edward Hebert School of medicine Uniformed Services University of Health Science Bethesda, Maryland

HOSPITAL APPOINTMENTS

1996-2003	Burn Center Director Shands Burn Center at the University of Florida Gainesville, Florida
1995-1996	Chief, Clinical Division U.S. Army Institute of Surgical Research Fort Sam Houston, Texas
1994-1995	Chief, Burn Study Branch U.S. Army Institute of Surgical Research Fort Sam Houston, Texas
1991-1994	Staff Surgeon U.S. Army Institute of Surgical Research Fort Sam Houston, Texas
1985-1986	General Medical Officer U.S. Army Institute of Surgical Research Fort Sam Houston, Texas

NATIONAL COMMITTEES

American Burn Association

2003-2004	Interim ABA Region IV Chairman
2002-present	Ad Hoc Committee for Disaster Response Planning
2001-present	Organization and Delivery of Burn Care, Chair
2000-present	ABLS Advisory Committee
2000-2003	Committee on Government Affairs
1998-2003	Region IV Chairman, ABA
1998-2003	Regionalization Committee, Region IV Southeast
1994-1996	Regionalization Committee, Region XII Military
1994-2000	Organization and Delivery of Burn Care

American Board of Surgery

2002	Associate Examiner, Jacksonville, Florida

STATE AND LOCAL COMMITTEES

1999-present	Member, Required Criteria for Consultation and Transfer Sub-Committee Trauma Program, Bureau of Emergency Medical Services, Florida Department of Health
1999-2004	Team Leader, Southeast Region Burn Specialty Team, National Disaster Medical System
1999-2001	Secretary, Southeast Burn Foundation
1997-1999	Chairman, Southeast Burn Foundation
1995-1996	Southwest Texas Regional Advisory Council
1995-1996	Greater San Antonio Hospital Council Critical Care Transfer Coordinating Board

INSTITUTIONAL COMMITTEES

2002-present	Shands HealthCare ICU Improvement Committee
2001-present	Informed Consent Committee, Shands Hospital, University of Florida College of Medicine
2000-2001	Chairman, Search Committee, Division of General Surgery, Shands Hospital, University of Florida, College of Medicine
1999-present	Chairman, Search Committee, Division of Burn Surgery, Shands Hospital, University of Florida, College of Medicine Faculty
1996-present	Chairman, Burn Center QI Committee Shands Hospital, Gainesville, Florida
1996-present	Infection Control Committee, Shands Hospital, Gainesville, Florida
1996-2000	Pharmacy and Therapeutics Committee Shands Hospital, Gainesville, Florida
1997-2000	Faculty Senate University of Florida, Gainesville, Florida
1997-1997	Level I Trauma Work Group Shands Hospital, Gainesville, Florida
1995-1996	Graduate Medical Education Committee Brooke Army Medical Center, Fort Sam Houston, Texas
1995-1996	Multidisciplinary Trauma Committee Brooke Army Medical Center, Fort Sam Houston, Texas
1994-1996	U.S. Army Institute of Surgical Research Council Fort Sam Houston, Texas
1994-1996	Chairman, Infection Control Committee, U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas
1993-1996	Hospital Credentials Committee, Brooke Army Medical Center, Fort Sam Houston, Texas
1992-1996	Animal Use Committee, U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas
1991-1992	Surgical Quality Assurance Committee, Brooke Army Medical Center, Fort Sam Houston, Texas
1990-1992	Animal Use Committee, Brooke Army Medical Center, Fort Sam Houston, Texas

SOCIETY MEMBERSHIPS

Florida Committee on Trauma, 2002
Alachua County Medical Society, 1996
Florida Surgical Society, 1996
American College of Surgeons, Fellow, 1994
The Society of University Surgeons, 2000
American Association for the Surgery of Trauma, 1995
Association for Academic Surgery, 1992
Surgical Infection Society, 1995
Society of Critical Care Medicine, 1991
Society of American Gastrointestinal Endoscopic Surgeons, 1991
American Burn Association, 1991
International Society for Burn Injuries, 1993
American Trauma Society, 1995
Wound Healing Society, 1999
South Texas Chapter, American College of Surgeons, 1994-1996
San Antonio Surgical Society – 1994-1996
International Association for the Surgery of Trauma and Surgical Intensive Care, 1996
International Association for Surgical Metabolism and Nutrition, 1999
Shock Society
International Society of Surgery – Société Internationale De. Chirurgie ISS/SIC, 1996
American Society for Parenteral and Enteral Nutrition, 1999
Eastern Association for the Surgery of Trauma, 1998
Association for the Advancement of Wound Care, 2001
Venezuelan Surgical Society (honorary member), 2000
Argentinian Burn Society (honorary member), 2001
American Board of Surgery Associate Examiner, 2001

VISITING PROFESSORSHIPS

1. Department of Surgery, Temple University, Philadelphia, Pennsylvania, May 14, 2003.
2. Cook County Hospital, Burn Center, Chicago, Illinois, May 18, 2001.
3. Profesore Internationale Invitado, VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, July 24-26, 1997
4. Department of Surgery, University of North Dakota, January 29, 1997
5. Baton Rouge Regional Burn Center, Baton Rouge, Louisiana, September 17, 1992.

EDITORIAL POSITIONS

2002-present	Editor, *Yearbook of Surgery*, Section of Burns, Trauma and Critical Care
2000-present	Editorial Board, *Journal of Burn Care and Rehabilitation*
1993-present	Ad hoc editor, *Journal of Trauma*

FUNDING/SOURCE

Cosmesis and Donor Site Assessment Plus a Thin Split-Thickness Skin Graft

(STSG) Compared to Standard-Thickness STSG Alone in Treatment of Full-Thickness Burn Wounds, LifeCell Corporation, 1998–complete, $15,000.

A Phase II Randomized, Double Blind, Placebo-Controlled, Multiple-Dose, Parallel Group, Multi-Center Study of the Effects of PB005 on Reepithelialization of Donor Sites in Patients with Burns Which Require Skin Grafting, Pharmadigm, 1998-complete, $20,728.00.

An Open Label Study to Evaluate the Incidence of Wound Infection in Patients Requiring a Temporary Covering for Excised Burn Wounds, Advanced Tissue Sciences, 1998-complete, $47,500.00.

T32 Shock/Trauma Training Grant, NIH, 1999-2003, $306,233, Clinical Mentor, Primary Investigator, Lyle Moldawer, PhD.

A Randomized Feasibility Study to Determine the Appropriate Number and Schedule of Application of a Collagen Matrix Containing Allograft Cells for the Treatment of Venous Ulcers, Ortec International, Inc., 2/3/99 – complete, $57,500.00.

Controlled Randomized Multi-center Study of the Effects of a Composite Cultured Skin Containing a Collagen Matrix Seeded with Allograft Cells on the Management of Split Thickness Donor Sites in Burn Patients, Ortec International, Inc., 7/21/99-complete, $38.750.00.

A Multi-center, Matched-Wound, Randomized, Open-Label Study to Compare the Healing Time of Acticoat© Silver-coated Dressing Compared with Xeroform Dressing in the Treatment of Partial-thickness Donor Site Wounds, Westaim Biomedical, Inc., 8/21/99-complete, $82,968.75.

A Multicenter, Retrospective Chart and Database Review of Patients with Toxic Epidermal Necrolysis Syndrome, 1/1/00-4/8/01.

A Randomized, Controlled, Within-patient-paired Study to Compare the Effectiveness of TransCyte™ and Biobrane© in the Treatment of Mid-Dermal to Indeterminate Depth Burn Wounds, 5/17/00-complete, $47,500.00.

A Molecular Analysis of Burn and Chronic Wound Healing, 6/1/00-present.

A Multicenter, Retrospective Chart and Database Review of Subjects with Tens/Stevens-Johnson Syndrome, 6/16/00-complete.

Clinical Evaluation of Regranex© (becaplermin) Gel 0.01% for the Treatment of Full Thickness Diabetic Neuropathic Foot Ulcers, 6/19/00-complete, $75,000.00.

Measurement of Burn Wound Elasticity Using Biomechanical Tissue Characterization, BTC-2000, 7/14/00-complete, $4,000.00.

Molecular Analysis of Burn and Wound Tissue Collected from Various Patients at Different Stages of Healing, 8/3/00-present.

Pilot Prospective Clinical Assessment of the Impact of Acticoat Silvercoated Antimicrobial Dressings on Cytokines and MMP's in Non-healing Wounds, 9/20/00 –complete, $50,440.00.

A Multicenter Clinical Trial of the Effects of Topical Application of Cerium Nitrate/Silver Sulfadiazine Cream Versus Silver Sulfadiazine Cream Alone in the Treatment of Burn Patients, 9/26/00-present, $31,500.00.

HGS KGF-2-WHO4-A Randomized, Double-blinded, Parallel-Group, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Repifermin (KGF-2) in Subjects with Venous Ulcers, 10/00-present, $167,955.00. Co-investigator, Primary Investigator, Gloria Chin, MD.

Treatment of Diabetic Foot Ulcers With A Protease Inhibitor, Doxycycline, 11/15/00, $150,000. VA Grant, Co-investigator, Primary Investigator, Gloria Chin, MD.

Protocol #AI 464-025: A Randomized, Double-blind, Multi-center, Comparative Phase III Study of Intravenous BMS-284756 with or without Oral BMS-284756 Follow-up vs Intravenous Piperacillin/Tazobactam with or without Oral Amoxicillin/Clavulanate Follow-up in the Treatment of Complicated Skin and Skin Structure Infections, 01/2001-complete, $47,500.00.

A Multicenter, Retrospective Chart and Database Review of Patients Treated for Lightning Injury, 6/15/01-complete.

A Multicenter, Retrospective Chart and Database Review of Subjects with Purpura Fulminans, 6/16/01-4/23/02.

Microarray Analysis of Gene Expression in Pediatric and Adult Post-burn Hypertrophic Scars, International Association of Fire Fighters Burn Foundation, 2002-present, $25,000.

A Dose Escalating Phase I Study of ADPDGF-BGAM in the Treatment of Diabetic Ulcers of the Lower Extremity, 8/2002-present, $218,166.25.

Enzymatic Debridement in Burn Patients: A Comparison to Standard of Care, 12/06/02-present, $ 34,440.00.

Evaluation of the Efficacy of the V.A.C. on Management of Acute Hand Burns, 1/6/03-present, $37,563.00.

PUBLICATIONS

Publications

1. Schultz GS, Barillo DJ, Mozingo DW, Chin GA. Wound Bed Preparation and a Brief History of TIME. *International Wound Journal* 1(1)19-32, 2004.

2. Still J, Glat P, Silverstein P, Griswold J, Mozingo D. The Use of a Collagen Sponge/Living Cell Composite Material to Treat Donor Sites in Burn Patients. *Burns* 29(8)837-841, 2003.

3. Paddock HN, Schultz GS, Baker HV, Varela JC, Beierle EA, Moldawer LL, Mozingo DW. Analysis of Gene Expression Patterns in Human Postburn

Hypertrophic Scars. *J Burn Care & Rehab.* November/December 24(6)371-377, 2003.

4. Warner PM, Kagan RJ, Yakuboff KP, Kemalyan N, Palmieri TL, Greenhalgh DG, Sheridan RL, Mozingo DW, Heimback DM, Gibran NS, Engrav L, Saffle JR, Edelman LS, Warden DG. Current Management of Purpura Fulminans: A Multicenter Study. *J Burn Care & Rehab.* May/June 24(3)119-126, 2003.

5. Tasaki O, Mozingo DW, Dubick MA, Goodwin CW, Yantis LD, Pruitt BA Jr. Effects of Heparin and Lisofylline on Pulmonary Function After Smoke Inhalation Injury in an Ovine Model. Crit Care Med. 30(3) 637-643, 2002.

6. Dubick MA, Carden SC, Jordan BS, Langlinais PC, Mozingo DW. Indices of antioxidant status in rats subjected to wood smoke inhalation and/or thermal injury. *Toxicology.* 176 (2002) 145-157.

7. Palmiere, TL, Greenhalgh DG, Saffle JR, Spence RJ, Peck MD, Jeng JC, Mozingo DW, Yowler CJ, Sheridan RL, Ahrenholz DH, Caruso DM, Foster KN, Kagan RJ, Voight DW, Purdue GF, Hunt JL, Wolf S, Molitor F, *J Burn Care & Rehab* March/April 23(2) 87-96, 2002.

8. Harrington DT, Mozingo DW, Cancio L, Bird P. Jordan B, Goodwin CW. Thermally injured patients are at significant risk for thromboembolic complications. *J Trauma.* March 50(3) 495-499, 2001.

9. Fukuzuka K, Edwards CK III, Clare-Salzler M, Copeland EM III, Moldawer LL, Mozingo DW: Glucocorticoid and fas ligand induced mucosal lymphocyte apoptosis after burn injury, *J Trauma.* October 49 (4) 710-71, 2000.

10. Fukuzuka K, Edwards CK III, Clare-Salzler M. Copeland EM III, Moldawer LL, Mozingo DW: Glucocorticoid-induced, caspase-dependent organ apoptosis early after burn injury, *Am J Physiol Regulatory Integrative Comp Physio.* 278: R1005-R1018, 2000.

11. Tasaki O, Goodwin C, Mozingo DW, Cioffi WG Jr, Ishihara S, Brinkley WW, Dublick MA, Smith RH, Srivastava O, Pruitt BA Jr: Selectin blockage worsened lipopolysaccharide-induced lung injury in a swine model, *J Trauma.* June, 46(6): 1089-1095, 1999.

12. Ishihara S, Ward JA, Tasaki O, Brinkley WW, Seraile LG, Pruitt BA Jr, Mozingo DW: Effects of long-term hemofiltration on circulating mediators and superoxide production during continuous endotoxin administration, *J Trauma.* May, 46(5): 894-89, 1999.

13. Ishihara S, Ward JA, Tasaki O, Pruitt BA Jr, Javors MA, Cassidy RA, Mozingo DW: Biphasic changes in left ventricular function during hyperdynamic endotoxemia, *Am J Physiol.* May, 276(5 Pt2):R1516-R1524, 1999.

14. Fukuzuka K, Rosenberg JJ, Gaines GC, Edwards CK III, Clare-Salzier M, McKay LD, Moldawer LL, Copeland EM III, Mozingo DW: Caspase-3-dependent organ apoptosis early after burn injury, *Ann Surg.* 229(6), 1999.

15. Mozingo DW: Treatment of Burns, Current Surgery, Vol 55(6), July/August 1998.

16. Fukuzuka K, Moldawer LL, Mozingo DW: Increased organ apoptosis early after burn is limited to lymphoid tissues and is TNFα independent. American College of Surgeons, Surgical Forum, Vol XLIX: 102-104, 1998.

17. Ishihara S, Ward JA, Tasaki O, Pruitt BA Jr, Goodwin CW Jr, Mozingo DW, Cioffi WG Jr: Inhaled nitric oxide prevents left ventricular impairment during endotoxemia, *J Appl Physiol.* 85(6): 2018-24, 1998.

18. Tasaki O, Mozingo DW, Ishihara S, Brinkley WW, Johnson AA, Smith RH, Srivastava O, Mason AD, Pruitt BA Jr., Cioffi WG Jr: Effect of sulfo lewis C on smoke inhalation injury in an ovine model, *Crit Care Med.* 26(7): 1238-1243, 1998.

19. Yowler CW, Mozingo DW, Ryan JC, Pruitt BA Jr: Factors contributing to delayed extremity amputation in burn patients. *J Trauma.* 45(3): 522-526, 1998.

20. Tasaki O, Goodwin CW, Saitoh D, Mozingo DW, Ishihara S, Brinkley WW, Cioffi WG Jr, Pruitt BA Jr, Effects of burns on inhalation injury. *J Trauma* 43(4): 603-607, 1997.

21. Barillo DJ, Harvey KD, Hobbs CL, Mozingo DW, Cioffi WG, Pruitt BA Jr: Prospective outcome analysis of a protocol for the surgical and rehabilitative management of burns to the hands. *Plast. Reconstr. Surg.* 100: 1442, 1997.

22. Cancio LC, Mozingo DW, Pruitt BA Jr: Administering affective emergency care for severe thermal injuries. *J Crit Illness.* 12(2): 85-95, 1997.

23. Cancio LC, Mozingo DW, Pruitt BA Jr: The technique of fluid resuscitation for patients with severe thermal injuries. *J Crit Illness.* 12(3): 193-199, 1997.

24. Cancio LC, Mozingo DW, Pruitt BA Jr: Strategies for diagnosing and treating asphyxiation and inhalation injuries. *J Crit Illness.* 12(4): 217-226, 1997.

25. Barillo DJ, Dickerson EE, Cioffi WG, Mozingo DW, Pruitt BA Jr: Pressure-controlled ventilation for the long-range aeromedical transport of patients with burns. *J Burn Care Rehabil.* 18(3): 200-205, 1997.

26. Mozingo DW, McManus AT, Kim SY, Pruitt BA Jr: The incidence of bacteremia following burn wound manipulation in the early postburn period. *J Trauma.* 42(6): 1006-1011, 1997.

27. Hansbrough JF, Mozingo DW, Kealey GP, David M, Gidner A, Gentzkow GD: Clinical trials of a biosynthetic temporary skin replacement, Dermagraft-transitional covering, compared to cryopreserved human cadaver skin for temporary coverage of excised burn wounds. *J Burn Care Rehabil.* 19(1): 43-51, 1997.

28. Harvey KD, Barillo DJ, Hobbs CL, Mozingo DW, Fitzpatrick JC, Cioffi WG, McManus WF, Pruitt BA Jr: Computer-assisted evaluation of and arm function after thermal injury. *J Burn Care Rehabil.* 17(2): 176-180, 1996.

29. Kelemen JJ III, Cioffi WG Jr, Mason AD Jr, Mozingo DW, McManus WF, Pruitt BA Jr; Effect of ambient temperature on metabolic rate following thermal injury, *Ann Surg.* 223(4): 406-12, 1996.

30. Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Peritoneal lavage in the diagnosis of acute surgical abdomen following thermal injury, *J Trauma* 38(1): 5-7, 1995.

31. Mozingo DW, Pruitt BA Jr: Infectious complications after burn injury, Current Opinions in Surgical Infections 2:69-75, 1994.

32. Mozingo DW, Barillo DJ, Pruitt BA Jr: Acute resuscitation and transfer management of thermally injured patients, Trauma Quarterly 11(2): 94-113, 1994.

33. Mozingo DW, Walters MJ, Otchy DP, Rosenthal D: Surgical pros and cons, SGO 176:81, 1993.

34. Mozingo DW, Otchy DP, Walters MJ, Rosenthal D: Properitoneal synthetic mesh repair of recurrent inguinal hernias: follow-up of 100 repairs, SGO 174:33-35, 1992.

35. Musio F, Mozingo DW, Otchy DP: Multiple, giant fibroadenoma, *American Surgeon.* 57: 438-441, 1991.

36. Rochon RB, Mozingo DW, Weigelt JA: New modes of mechanical ventilation, Surg Clin NA 71: 843-858, 1991.

37. Ducey JP, Mozingo DW, Lamiell JM, Gueller GE: A comparison of the cerebral and cardiovascular effects of complete resuscitation with isotonic and hypertonic saline, hetastarch and whole blood following hemorrhage, *J Trauma.* 29(11): 1510-1519, 1989.

38. Mozingo DW, Smith AA, McManus WF, Pruitt BA Jr, Mason AD: Chemical burns, *J Trauma.* 28(5): 642-647, 1988.

39. Vigersky RA, Mozingo DW, Eil C, Purohit V, Burton J: The antiandrogenic effects of Delta-4 – testolactone (Teslac) in vivo in rats and in vitro in human cultured fibroblasts, rat mammary carcinoma cells and rat prostrate cytosol, *Endocrinology.* 110(1): 214-219, 1982.

Monographs

1. Mozingo DW, McManus AT, Pruitt BA Jr: Appropriate use of parenteral antibiotics in managing burns. Surgical Infections Index and Reviews, Vol I, Number 1, July 1993, pp 1, 17-20.

2. Mozingo DW: Quality improvement guidelines for burn center verification, http://ameriburn.org/pub/verification_QI%20Programs, htm, American Burn Association Web Page

Book Chapters

1. Mozingo DW: Trauma. In: Copeland EM, Bland KI, Cerfolio RJ, Daly JM, Eberlein TJ, Howard RJ, Luce EA, Mozingo DW, Seeger JM, eds. *Year Book of Surgery 2004*. Mosby, Inc., 2003, pp25-54.

2. Mozingo DW: Burns. In: Copeland EM, Bland KI, Cerfolio RJ, Daly JM, Eberlein TJ, Howard RJ, Luce EA, Mozingo DW, Seeger JM, eds. *Year Book of Surgery 2004*. Mosby, Inc., 2003, pp55-84.

3. Mozingo DW. Critical Care. In Copeland EM, Bland KI, Cerfilio JR, Daly JM, Eberlein TJ, Howard RJ, Luce EA, Mozingo DW, Seeger JM, eds. *Year Book of Surgery 2004*, Mosby, Inc. 2003, pp85-112.

4. Marko P, Layon AJ, Caruso L, Mozingo DW, Gabrielli A. Burn Injuries. *Curr Opin Anaesthesiol.* 16:183-191, 2003.

5. McAuliffe PF, Mozingo DW. Problems in General Surgery. *Inhalation Injury and Ventilator Management.* 20(1) 97-105, 2003.

6. Mozingo DW: Trauma. In: Copeland EM, Bland KI, Cerfolio RJ, Daly JM, Eberlein TJ, Howard RJ, Luce EA, Mozingo DW, Seeger JM, eds. *Year Book of Surgery 2003*. Mosby, Inc., 2003, pp21-48.

7. Mozingo DW: Burns. In: Copeland EM, Bland KI, Cerfolio RJ, Daly JM, Eberlein TJ, Howard RJ, Luce EA, Mozingo DW, Seeger JM, eds. *Year Book of Surgery 2003*. Mosby, Inc., 2003, pp49-80.

8. Mozingo DW. Critical Care. In Copeland EM, Bland KI, Cerfilio JR, Daly JM, Eberlein TJ, Howard RJ, Luce EA, Mozingo DW, Seeger JM, eds. *Year Book of Surgery 2003*, Mosby, Inc. 2003, pp81-105.

9. Mozingo DW, Cioffi WG Jr, Pruitt BA Jr: Burns. In: Bongard FS, Sue DY, eds. *Current Critical Care Diagnosis &Treatment.* 2nd ed.: Lange Medical Books/McGraw-Hill, 2002, pp 799-828.

10. Mozingo DW. Thermal Injury. In: Bland KL, ed. *The Practice of General Surgery*: W.B. Saunders Company, Philadelphia, Pennsylvania, 2002, pp 90-100.

11. Mozingo DW, Mason AD. Hypophosphatemia. In: Herndon DN ed. *Total Burn Care.* 2nd ed. Kent, United Kingdom: Harcourt Publishers Limited, 2002, pp 309-315.

12. Hartsmamnsruber, Mozingo, Layon. Thermal Injuries: Pathophysiology and Anesthetic Considerations. In: Kirby RR, Gravenstein N, Lobato E. Gravenstein JS, eds. *Clinical Anesthesia Practice.* 2nd ed.: WB Sanders, 2001, pp 752-769.

13. Mozingo DW. Thermal Injury. In: Corson JD, Williamson RCN, eds. *Surgery*: Mosby International, 2001, (2), pp 13.1-13.12.

14. Mozingo DW. Tratamiento de las quemaduras electricas, (Treatment of Electrical Burns) In: Zapata Sirvent RL, Del Reguero A, Leon RK, eds. *Autualization en Quemaduras. Rumbo at 2000*: ATEPROCA C.A., Caracas, October 1999, pp 57-59.

15. Mozingo DW, Pruitt BA Jr. Burn Trauma and Surgery. In: Niederhuber JE, ed. *Fundamentals of Surgery*: Norwalk CT: Appleton & Lange, 1998, pp 182-200.

16. Mozingo DW. Surgical Management. In: Carrougher GJ, ed. *Burn Care and Therapy*: Boston, Massachusetts: Mosby Yearbook, 1998, pp 233-248.

17. Mozingo DW. Manejo del Dolor in el Paciente Quemado. (Pain Management in Burn Patients) In: Sirvent RLZ, Del Reguero A, eds. *Actualización en el Tratamiento de las Quemaduras, tomo II*: ATEPROCA, C.A., Caracas, Venezuela, 1997, pp 118-123.

18. Mozingo DW. Manejo quirúrgico de las Quemaduras. Excisión e injerto. (Surgical Management of Burns. Excision and Grafting) In: Sirvent RLZ, Del Reguero A, eds. *Actualización en el tratameinto de las quemaduras, tomo II*: ATEPROCA, C.A., Caracas, Venezuela, 1997, pp 59-65.

19. Mozingo DW. Prevención y tratamiento de las infecciones in las areas quemadas. (Prevention and Treatment of Infection in Burn Wounds) In: Sirvent RLZ, Del Reguero A, eds. *Actualización en el tratameinto de las quemaduras, tomo II*: ATEPROCA, C.A., Caracas, Venezuela, 1997, pp 47-58.

20. Mozingo DW. Estrategias para el diagnóstico y tratamiento de las quemaduras por inhalación. (Strategies for the Diagnosis and Treatment of Inhalation Injury) In: Sirvent RLZ, Del Reguero A, eds. *Actualización en el tratamiento de las quemaduras, tomo II*: ATEPROCA, C.A., Caracas, Venezuela, 1997, pp 37-46.

21. Mozingo DW. Manejo de la fase aguda de las quemaduras en ninos. (Fluid Resuscitation in Burned Children) In: Sirvent RLZ, Del Reguero A, eds. *Actualización en el tratamiento de las quemaduras, tomo II*: ATEPROCA, C.A., Caracas, Venezuela, 1997, pp 5-8.

22. Mozingo DW, McManus AT, Pruitt BA Jr. Infections of burn wounds. In: Bennet JV and Brackman PS, eds. *Hospital Infections*, Philadelphia, PA: Lippencott-Raven, 1997, pp 587-597.

23. Mozingo DW, Mason AD Jr. Hypophosphatemia. In: Herndon DN, ed. *Total Burn Care.* London: WB Saunders Company Ltd, 1996, pp 259-264.

24. Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr. Burns, In: FS Bongard, SY Sue, ed. *Current Diagnosis and Treatment in Critical Care.* Norwalk, CT. Appleton-Lange, 1994, pp 657-685.

25. Mozingo DW, Pruitt BA Jr: Burn Injury. In: L Rosen, JA Weigelt, Eds. *War Surgery*. Norwegian Army Medical Corps Manual on Emergency Surgery 85-100, 1994.

Book/Journal Reviews

Surgical Infections: Diagnosis and Treatment. Critical Care Medicine 23(8):1453-1454.

Treatment of Burns. Current Surgery 55(6) July/August 1998:224-238.

Abstracts

1. Palmieri TL, Caruso DM, Foster KN, Cairns BA, Gamelli RL, Mozingo DW et al: Blood Transfusion Practices in Major Burn Injury: A Multicenter Study. Proceedings of the American Burn Association 36th Annual Meeting, Vancouver, British Columbia, March 23-26, 2004, abstract 1.

2. Wolf SE, Edelman LS, Kemalyan NA, Donison L, Cross JM, Underwood M, Palmiere TL, Lawless M, Spence CW, Goodwin CW, Noppenberger D, Voigt DW, Edwards P, Caruso DM, Foster KN, Hildebrand B, Jeng JC, Crean DA, Purdue GF, Hunt JL, Burris A, Warner PM, Hatfield S, Klein RL, Baker R, Cairns BA, Kessler M, Yowler CJ, Tutolo W, Mozingo DW, et al. Effects of Oxandrolone on Length of Hospital Stay in the Severely Burned: A Multi-Center Prospective Randomized Double-Blind Trial. Proceedings of the American Burn Association 36th Annual Meeting, Vancouver, British Columbia, March 23-26, 2004, abstract 25.

3. Molnar JA, Heimback DM, Tredget EE, Hickerson WL, Still JM, Luterman A, Lozano DD, Mozingo DW. Prospective, Randomized, Controlled, Julticenter Trial Applying Subatmospheric Pressure to Acute Hand Burns: An Interim Report. Proceedings of the American Burn Association 36th Annual Meeting, Vancouver, British Columbia, March 23-26, 2004, abstract 66.

4. Perrin K, Thigpin T, Barillo DJ, Mozingo DW, Schultz GS, Blalock T. The Effect of a Silver Coated Antimicrobial Barrier Dressing on Healing of Venous Stasis Ulcers: Preliminary Results of a Randomized Controlled Clinical Trial. The John A. Boswick, MD Burn and Wound Care Symposium, Maui, Hawaii, February 23-27, 2004, abstract 42.

5. Pruitt BA Jr, Goodwin CW, Mozingo DW, Loring WR III, Cioffi WG, Becker WK: Planning and Delivery of Burn Care in Peace and War. Proceedings of the 11th Quadrennial Congress of the International Society for Burn Injuries, Seattle, Washington, August 11-16, 2002, abstract 7.

6. Mozingo DW, Ben-David K, Perrin K, Schultz GS: Comparison of the Biomechanical Properties of Burns Grafted with Conventional Split Thickness Skin vs. Integra™ Artificial Skin. Proceedings of the 11th Quadrennial Congress of the International Society for Burn Injuries, Seattle, Washington, August 11-16, 2002, abstract 184.

7. Paddock HN, Schultz GS, Varela JC, Beierle EA, Moldawer LL, Mozingo DW: Differential Gene Expression in Human Post-Burn Hypertrophic Scars Compared to Normal Skin. Proceedings of the 2002 Joint Conference of the Wound Healing Society and the European Tissue Repair Society, Baltimore, Maryland, May 28-June 1, 2002, abstract 115, page 23.

8. Stechmiller JK, Paddock HN, Gowda S, Mozingo DW, Chin GA, Porter T, Schultz GS: Biochemical Analysis of Wound Fluid from Chronic Wounds Treated with VAC. Proceedings of the 2002 Joint Conference of the Wound Healing Society and the European Tissue Repair Society, Baltimore, Maryland, May 28-June 1, 2002, abstract 121, page 21.

9. Paddock HN, Schultz GS, Perrin KJ, Moldawer LL, Wright B, Mozingo DW: Clinical Assessment of Silver-Coated Antimicrobial Dressing on MMPs and Cytokine Levels in Non-Healing Wounds. Proceedings of the 2002 Joint Conference of the Wound Healing Society and the European Tissue Repair Society, Baltimore, Maryland, May 28-June 1, 2002, abstract 120, page 21.

10. Paddock HN, Schultz GS, Varela JC, Baker HV, Beierle EA, Mozingo DW, Moldawer LL: Microarray Analysis of Gene Expression Patterns in Human Post-Burn Hypertrophic Scars Compared to Normal Skin. A Multicenter Study. Proceedings of the American Burn Association 34th Annual Meeting, Chicago, Illinois, April 24-27, 2002, abstract 114, page S96.

11. Warner PM, Kagan RJ, Palmieri TL, Greenhalgh DG, Sheridan RL, Kemalyan N, Heimback DM, Gibran NS, Saffle JR, Edelman LS, Mozingo DW, Warden DG: Current Management of Purpura Fulminans: A Multicenter Study. Proceedings of the American Burn Association 34th Annual Meeting, Chicago, Illinois, April 24-27, 2002, abstract 80, page S80.

12. Mozingo DW, Paddock HN, Perrin KJ, Moldawer LL, Wright B, Burrell R, Schultz GS: The Effect of Silver-Coated Antimicrobial Dressings On Matrix Metalloprotease (MMP) Levels in Lower Extremity Venous Stasis Ulcers. The John A. Boswick, MD Burn and Wound Care Symposium, Maui, Hawaii, February 18-22, 2002, program in order of presentation, page 32.

13. Hudson D, Mozingo DW: Successful Development of a Hospital-Base Wound Healing Program within a Burn Center Facility. The John A. Boswick, MD Burn and Wound Care Symposium, Maui, Hawaii, February 18-22, 2002, program in order of presentation, page 60.

14. Gaines GC, Perrin KJ, Mozingo DW: Lightning-Related Injury: Pathophysiology, Morbidity and Mortality. Proceedings of the 14th Annual Regional Burn Seminar, Chattanooga, Tennessee, 7-9 December, 2002, page 33.

15. Perrin KJ, Gaines GC, Ben-David K, Schultz GS, Mozingo DW: Comparison of the Biomechanical Tissue Characterization System (BTC-2000) on Burn Scars versus Standard Clinical Scar Assessments using the Vancouver Scar Scale (VSS). Proceedings of the 14th Annual Regional Burn Seminar, Chattanooga, Tennessee, 7-9 December 2002, page 33.

16. Perrin KJ, Meyer CL, Manion KL, Roque DR, Langer KA, Wingard JR, Mozingo DW: Management of the cutaneous manifestations of graft vs. host disease using burn wound treatment protocols. Proceedings of the American Burn Association 33rd Annual Meeting, Boston, Massachusetts, 18-21 April 2001, abstract 72, page S133.

17. Mozingo DW: Comparison of the biomedical properties of burns grafted with conventional split-thickness graft vs. integra®. Proceedings of the John A. Boswick, MD, Burn & Wound Care Symposium, Maui, Hawaii, February 19-23, 2001, program in order of presentation, page 34.

18. Mozingo, DW: Successful wound closure in epidermolysis bullosa dystrophica using integra® artificial skin for dermal replacement. Proceedings of the John A. Boswick, MD, Burn & Wound Care Symposium, Maui, Hawaii, February 19-23, 2001, program in order of presentation, page 24.

19. Hudson D, Mozingo DW: Using the intranet to improve patient care: policies and procedures on line. Proceedings of the 13th Annual Regional Burn Seminar. Atlanta, GA, December 1-3, 2000, page 57.

20. Beard J, Mozingo DW: Early transfer to rehabilitation: improved length of stay, decreased costs and maximized functional outcomes. Proceedings of the 13th Annual Regional Burn Seminar, Atlanta, GA, December 1-3, 2000, page 52.

21. Hudson D, Popp J, Mozingo DW: A new sister burn center exchange program: Shands Burn Center at the University of Florida, Gainesville, Florida and the Burn Foundation Burn Unit, of hospital Aleman, Buenos Aires, Argentina. Proceedings of the 12th Annual Regional Burn Seminar, Winston-Salem, NC, December 3-5, 1999, page 72.

22. Harrington DT, Burke B, Bird P, Jordan BS, Mozingo DW, Barillo DJ, Shirani KZ, Goodwin CW: Thermally injured patients are at significant risk of thromboembolic complications. Proceedings of the 31st Annual Meeting of the American Burn Association, Lake Buena Vista, FL, March 24-27,1999, abstract 83, page S178.

23. Fukuzuka K, Rosenberg JJ, Moldawer LL, Gaines GC, Mozingo DW, Copeland EM III: Lymphoid organ apoptosis after burn injury is caspase-3 dependent. Proceedings of the One Hundred Tenth Annual Session of the Southern Surgical Association, Palm Beach, FL, December 6-9, 1998, page 43.

24. Fukuzuka K, Rosenberg JJ, Gaines GC, Moldawer LL, Copeland EM III, Mozingo DW. Increased caspase-3 dependent organ apoptosis early after burn injury. Proceedings of the 11th Annual Regional Burn Seminar, Gainesville, FL, December 4-6, 1998, page 53.

25. Huddleston BA, Hanson C, Mozingo DW: Factors influencing compliance with pressure garment use. Proceedings of the 11th Annual Regional Burn Seminar, Gainesville, Fl, December 4-6, 1998, page 48.

26. Fukuzuka K, Moldawer LL, Mozingo DW: Increased organ apoptosis following burn injury. Proceedings of the 21st Annual Conference on Shock, San Antonio, TX, June 1998, abstract 12.

27. Ishihara S, Ward JA, Pruitt BA Jr, Mozingo DW: Effects of hemofiltration on left ventricular impairment in an awake swine model of sepsis. Proceedings of the 21st Annual Conference on Shock, San Antonio, TX, June 1998, abstract 82.

28. Dubick MA, Jordan BS, Carden SC, Crissman K, Hatch, GE Langlinais P, Mozingo DW: Antioxidant status of bronchoalveolar lavage fluid and lungs from rats subjected to burn and/or smoke inhalation. Toxicologist 42:348, 1998.

29. Mozingo DW: Burn care strategies. Proceedings of the Critical Care Update, 1997, Orlando, Florida, 22-26 November 1997, page 73.

30. Dubick MA, Mozingo DW, Jordan BS, Carden SC: Evaluation of bronchial alveolar lavage fluid and lungs from rats subjected to a 20% tbsa scald burn and/or smoke inhalation. Proceedings of the Fourth Sino-American Conference on Burns and Trauma, 29 September 2-October 1997, page 98.

31. Ishihara S, Ward JA, Tasaki O, Brinkley WW, Seraile LG, Pruitt BA Jr, Mozingo DW: Effects of long term hemofiltration of endotoxin, cytokine, eicosanoid and superoxide production during sepsis. Proceedings of the AAST/JAAM Joint Meeting, Kamuela, Hawaii, 24-27 September 1997, page 266.

32. Tasaki O, Goodwin CW, Mozingo DW, Brinkley WW, Dubick AM, Pruitt BA Jr: Effects of heparin and lisofylline on pulmonary function following severe smoke inhalation injury in an ovine model. Proceedings of the AAST/JAAM Joint Meeting, Kamuela, Hawaii, 24-27 September 1997, page 305.

33. Ishihara S, Tasaki O, Pruitt BA Jr Cioffi W Jr, Ward J, Goodwin C Mozingo D: Nitric Oxide inhalation prevented left ventricular impairment in an awake porcine model simulating human septic shock. Proceedings of the 17th Annual Meeting of the Surgical Infection Society, Pittsburgh, PA, 1-3 May 1997, page 86.

34. Yowler CJ, Mozingo DW, Ryan JB, Pruitt BA Jr: Factors contributing to delayed extremity amputation in burn patients. Proceedings of the 29th Annual Meeting of the American Burn Association, New York, NY, 19-22 March 1997, page S151.

35. Harrington DT, Bird PE, Mozingo DW, Shirani KZ, Goodwin CW: An increased incidence of thromboembolic complications in thermally injured patients. Proceedings of the 29th Annual Meeting of the American Burn Association, New York, NY, 19-22 March 1997, page S109.

36. Tasaki O, Goodwin CW, Mozingo DW, Cioffi WG, Brinkley W, Dublick MA, Mason AD Jr, Pruitt BA Jr: The effect of burns on inhalation injury: a 5-day study. Proceedings of the 29th Annual Meeting of the American Burn Association, New York, NY, 19-22 March 1997, page S72.

37. Mozingo DW, McManus AT, Kim SH, Pruitt BA Jr: The incidence of bacteremia following burn wound manipulation in the early post-burn period. Proceedings of the 56th Annual Meeting of the Association for the Surgery of Trauma, Houston, Texas, 19-21 September 1996, paper 40, page 116.

38. Ishihara S, Ward JA, Tasaki O, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Left ventricular dysfunction in an awake porcine model simulating human hyperdynamic septic shock. Proceedings of the 15th Annual Meeting of the Surgical Infection Society, Milwaukee, WS, 24-27 April 1996, p12, page 91.

39. Dubick MA, Mozingo DW, Janssen CM, Carden SC, Joyner YS, Mason AD Jr, Pruitt BA Jr: Evidence of oxidative injury in rats following smoke inhalation injury. Toxicologist 30(1, Pt.2): 273, 1996.

40. Kelemen JJ III, Mozingo DW, Cioffi WG, Mason AD Jr, Pruitt BA Jr: Granulocyte colony stimulating factor (G-CSF) do not exacerbate lung injury following smoke inhalation in rats. Proceedings of the Annual Meeting of the South Texas Chapter of the American College of Surgeons, San Antonio, Texas, 14-16 March 1996.

41. Hansbrough JF, Mozingo DW, Kealey GP, Davis M. Gidner A, Gentzkow GD: Dermagraft-TC™ as a temporary covering for treatment of excised burn wounds. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 7, page 46.

42. Starks LJ, Harrington DT, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Extent of cutaneous exfoliation predicts metabolic rate in patients with TENS. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996. abstract 115, page 105.

43. Hidenrite D, Harrington DT, Mozingo DW, Pruitt BA Jr: Risk factors for the development of catheter-related urinary tract infection in burn patients. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 140, page 117.

44. Harrington DT, Hidenrite D, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Determinants of infection risk in the elderly burn patient. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 138, page 116.

45. Harrington DT, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Pre-existing medical conditions influence outcome in the elderly patient following thermal injury. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TX, 14-17, March 1996, abstract 36, page 60.

46. Voight DW, Harrington DT, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Evaluation of the effect of cirrhosis on the management of thermal injury. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 53, page 69.

47. Jordan B, Bird PE, Mozingo DW, Pruitt BA Jr: Barbeque grilling – reducing the risk of burn injury. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 223, page 155.

48. Wooten C Jr, Jordan B, Mozingo DW, Pruitt BA Jr: Priorities in the nursing care management of patients with severe exfoliative skin disease. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 114, page 104.

49. Barillo DJ, Stetz CK, Mozingo DW, Yowler CJ, Pruitt BA Jr: Why do children get burned? Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 104, page 79.

50. Barillo DJ, Harvey KD, Hobbs CL, Mozingo DW, Cioffi WG, Pruitt BA Jr: Prospective outcome analysis of a protocol for the surgical and rehabilitative management of burns of the hands. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 27, page 56.

51. Mozingo DW, Sheridan RL, Mason AD Jr, Pruitt BA Jr: Prevention of pulmonary thromboembolism in morbidly obese burn patients. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 51, page 68.

52. Tasaki O, Cioffi WG, Saitoh D, Mozingo DW, Ishihara S, Johnson AA, Mason AD Jr, Pruitt BA Jr: The effect of burns on inhalation injury. Proceedings of the 28th Annual Meeting of the American Burn Association, Nashville, TN, 14-17 March 1996, abstract 11, page 48.

53. Tasaki O, Cioffi W Jr, Mozingo D, Ishihara S, Brinkley W, Johnson A, Smith R, Srivastava, Mason A, Pruitt B Jr: Effect of sulfo lewis C. a putative ligand of selections on smoke inhalation injury in an ovine model. Proceedings of the 25th Annual Meeting of the Society of Critical Care Medicine, New Orleans, Louisiana, 5-9 February 1996, 24(1) A28.

54. Ishihara S, Ward J, Beausant LA, Tasaki O, Mozingo D, Mason A Jr, Pruitt BA Jr: Relationship between plasma tumor necrosis factor-alpha and left ventricular end diastolic dimension in an awake swine model of sepsis. Proceedings of the 25th Annual Meeting of the Society of Critical Care Medicine, New Orleans, Louisiana, 5-9 February 1996, 24(1) A28.

55. Hobbs CL, Barillo DJ, Harvey KD, Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Physical and Occupational Therapy support of a burn mass casualty incident: planning implications for future incidents. Proceedings of the 8th Annual Trauma Anesthesia and Critical Care Symposium, Baltimore, Maryland, 11-13 May 1995.

56. Barillo DJ, Hidenrite D, Stetz CK, Greenfield E, Mozingo DW, McManus WF, Pruitt BA Jr: Occupational exposure to bloodborne pathogens in the burn center – a serologic study of burn patients. Proceedings of the 8th Annual Trauma

Anesthesia and Critical Care Symposium, Baltimore, Maryland, 11-13 May 1995.

57. Kelemen JJ III, Martin RR, Barillo DJ, Mozingo DW, McManus WF, Pruitt BA Jr: Case Report: Streptococcal Fasciitis and Sepsis. Proceedings of the 47th Annual Meeting of the Southwestern Surgical Congress, San Antonio, Texas, 23-26 April 1995.

58. Swartz AL, Greenfield E, Mozingo DW, McManua WF, Pruitt BA Jr: Staff perceptions of a MASCAL and post-trauma symptoms. Proceedings of the 27th Annual Meeting of the American Burn Association, Albuquerque, NM, 19-22 April 1995, page 163.

59. Mozingo DW, McManus WF, Mason AD Jr, Pruitt BA Jr; Perioperative antibiotic use for burn surgery. Proceedings of the 27th Annual Meeting of the American Burn Association, Albuquerque, NM, 19-22 April 1995, page 212.

60. Allies WE, Mozingo DW, Fitzpatrick JC, Cioffi WG, McManus WF, Pruitt BA Jr: Increased humidification requirements of VDR ventilation. Proceedings of the 27th Annual Meeting of the American Burn Association, Albuquerque, NM, 19-22 April 1995, page 287.

61. Dubick MA, Janssen CM, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Combined smoke inhalation and thermal injury augments changes in extrapulmonary antioxidant status in rats. Proceedings of the 27th Annual Meeting of the American Burn Association, Albuquerque, NM, 19-22 April 1995, page 284.

62. Harvey KD, Barillo DJ, Hobbs CL, Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr; Computer-assisted evaluation of hand function following thermal injury. Proceedings of the 27th Annual Meeting of the American Burn Association, Albuquerque, NM, 19-22 April 1995, page 254.

63. Carrougher G, Cioffi WG, Mozingo DW, McManus WF, Pruitt BA Jr: A comparison of continuous cardiac output monitoring with bolus thermodilution cardiac output determinations in burn patients. Proceedings of the 9th Congress of the International Society for Burn Injuries, Paris, France, 27 June-1 July 1994, page 381.

64. Mozingo DW, Cioffi WG Jr, Becker WK, Mason AD Jr, Pruitt BA Jr: The effect of timing of administration of trinositol (PP56) on burn wound edema and albumin extravasation. Proceedings of the 9th Congress of the International Society for Burn Injuries, Paris, France, 27 June-1 July 1994, page 385.

65. Cassidy RA, Lyons VL, Coffey, Mozingo DW, Burleson DG, Mason AD Jr, Pruitt BA Jr: Myoglobinemia in thermal and electric burns: procedures, temporal differences and survival. J Mil Med Lab Sci 22(3):124 1993.

66. Mozingo DW, Cioffi WG, Mason AD Jr, Milner EA, McManus WF, Pruitt BA Jr: Initiation of continuous enteral feeding induces hypophosphatemia in thermally injured patients. Proceedings of the 35th World Congress of Surgery/International Society of Surgery/International Surgical Week, Hong

Kong, 22-27 August 1993, abstract 104.

67. Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: The use of peritoneal lavage to diagnose acute surgical abdomen following burn injury. Proceedings of the Third Sino-American Conference on Burns and Trauma, Guangzhou, China, 16-19 August 1993, page 191.

68. Mozingo DW, Rochon RB, Lamiell JM: The effect of dobutamine infusion on fluid volume requirements following hemorrhage. Circulatory Shock, Supplement 2, Page 11, 1993.

69. Mozingo DW, Cioffi WG, Vermillion DA, Mason AD Jr, Pruitt BA Jr: The management of femoral shaft fractures in thermally injured patients. Proceedings of the 25th Annual Meeting of the American Burn Association, Cincinnati, Ohio, March 1993, page 119.

70. Walton GF, Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Burns in children: a comparison of accidental and non-accidental injuries. The American Trauma Society, May 1992.

71. Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Peritoneal lavage in the diagnosis of acute surgical abdomen following thermal injury. Proceedings of the 24th Annual Meeting of the American Burn Association, Salt Lake City, Utah, April 1992, page 146.

72. Mozingo DW, Becker WK, Lamiell JM, Cioffi WG, Pruitt BA Jr: Pulmonary amino acid flux in critically ill surgical patients. Proceedings of the International Surgical Week, Stockholm, Sweden, August 1991, abstract 859, page 433.

73. Mozingo DW, Becker WK, Mason AD, Pruitt BA Jr: The significance of jaundice in burn patients. Proceedings of the International Surgical Week, Stockholm, Sweden, August 1991, abstract 539, page 355.

74. Mozingo DW, Ducey JP, Lamielli JM, Gueller GE: The effect of 6% saline on cerebral hemodynamics following hemorrhage. Society of Critical Care Medicine, June 1990.

75. Mozingo DW, Alverez JD: Spontaneous thoracobiliary fistula – a rare complication of an "asymptomatic: gallstone. The 42nd Annual Meeting of the Southwest Surgical Congress, April 1990.

76. Mozingo DW, Ducey JP, Lamielli JM, Gueller GE: The effect of 6% saline on cerebral hemodynamics following hemorrhage. Proceedings of the Society of Critical Care Medicine, New Orleans, Louisiana, 5-9 June 1989, 17(4) S147.

77. Mozingo DW, Missavage AE, McManus WF, Pruitt BA Jr: Acalculous cholecystitis diagnosed by Indium-III labeled leukocytic scanning in a severely burned patient. The 39th Annual Meeting of the Southwest Surgical Congress, April 1987.

Miscellaneous Publications

1. Mozingo DW: Quality improvement guidelines for burn center verification, http://ameriburn.org/pub/verification.htm, American Burn Association Web Page

EXHIBITS

1. McKinnon C, Dubose MA, Groher ME, Mann G, Mozingo, DW: Pattern of Dysphagia Recovery Following Thermal Burn Injury. Proceedings of the 12th Annual Dysphagia Research Society Meeting, San Francisco, CA 2-4 October, 2003.

2. Perrin KJ, Meyer CL, Manion KL, Roque DR, Langer KA, Wingard JR, Mozingo DW: Management of the cutaneous manifestations of graft vs. host disease using burn wound treatment protocols. Proceedings of the American Burn Association 33rd Annual Meeting, Boston, Massachusetts, 18-21 April 2001.

3. Ishihara S, Ward JA, Pruitt BA Jr, Mozingo DW: Comparison of two different parameters for elimination TNF_{α} from circulating blood by continuous hemofiltration during endotoxemia. Proceedings of the 29th Educational & Scientific Symposium Critical Care Medicine, Orlando, Florida, 11-15 February 2000.

4. Fukuzuka K, Moldawer LL, Mozingo DW: Increased organ apoptosis following burn injury. Proceedings of the 21st Annual Conference on Shock, San Antonio, TX, June 1998.

5. Ishihara S, Ward JA, Tasaki O, Brinkley WW, Seraile LG, Pruitt BA Jr, Mozingo DW: Effects of long term hemofiltration of endotoxin, cytokine, eicosanoid and superoxide production during sepsis. Proceedings of the AAST/JAAM Joint Meeting, Kamuela, Hawaii, September 24-27 1997.

6. Tasaki O, Goodwin CW, Mozingo DW, Brinkley WW, Dubick MA, Pruitt BA Jr: Effects of heparin and lisofylline on pulmonary function following severe smoke inhalation injury in an ovine model. Proceedings of the AAST/JAAM Joint Meeting, Kamuela, Hawaii, September 24-27 1997.

7. Ishihara S, Tasaki O, Pruitt B Jr, Cioffi W Jr, Ward J, Goodwin C, Mozingo D: Nitric oxide inhalation prevented left ventricular impairment in an awake porcine model simulating human septic shock. 17th Annual Meeting of the Surgical Infection Society. Pittsburgh, PA, 1-3 May 1997.

8. Allies WE, Mozingo DW, Pruitt BA Jr: Application of intrapulmonary percussive ventilation (IPV) therapy in patients with smoke inhalation. 28th Annual Meeting of the American Burn Association, 14-17 March 1996.

9. Cancio LC, Yowler CJ, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Gastrointestinal surgery following thermal injury. 28th Annual Meeting of the American Burn Association, 14-17 March 1996.

10. Sirak RM, Hobbs CL, Mozingo DW, Yowler CJ, Pruitt BA Jr: The pediatric travois net bed: a cost effective alternative to specialty high air-flow beds. 28th Annual Meeting of the American Burn Association, 4-17 March 1996.

11. Barillo DJ, Stetz CK, Mozingo DW, Yowler CJ, Pruitt BA Jr: Preventable burns associated with the misuse of gasoline. 28th Annual Meeting of the American Burn Association, 14-17 March 1996.

12. Hobbs CL, Barillo DJ, Jarvey DW, Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Physical and occupational therapy support of a burn mass casualty incident: planning implications for future incidents. 8th Annual Trauma Anesthesia and critical Care Symposium, Baltimore, Maryland, 11-13 May 1995.

13. Barillo DJ, Hidenrite D. Stetz CK, Greenfield E, Mozingo DW, McManus WF, Pruitt BA Jr: Occupational exposure to bloodborne pathogens in the burn center – a serologic study of burn patients. 8th Annual Trauma Anesthesia and Critical Care Symposium, Baltimore, Maryland, 11-13 May 1995.

14. Harvey KD, Barillo DJ, Hobbs CL, Mozingo DW, Cioffi WG, McManus WF, Pruitt BA Jr: Computer assisted evaluation of hand function following thermal injury. 27th Annual Meeting of the American Burn Association, Albuquerque, New Mexico, 19-22 April 1995.

15. Dubick MA, Janssen CM, Mozingo DW, Mason AD Jr, Pruitt BA Jr: Combined smoke inhalation and thermal injury augments changes in extrapulmonary antioxidant status in rats, 27th Annual Meeting of the American Burn Association, Albuquerque, New Mexico, 19-22 April 1995.

16. Allies WE, Mozingo DW, Fitzpatrick JC, Cioffi WG, McManus WF, Pruitt BA Jr: Increased humidification requirements of VDR ventilation. 27th Annual Meeting of the American Burn Association, Albuquerque New Mexico, 19-22 April 1995.

17. Mozingo DW, Rochon RB, Lamiell JM: The effect of dobutamine infusion on fluid volume requirements following hemorrhage. Annual Meeting of the Shock Society, Santa Fe, New Mexico, June 1993.

18. Mozingo DW, Becker WK, Cioffi WG Jr, McManus WF, Pruitt BA Jr: Pulmonary amino acid flux in critically ill surgical patients. International Surgical Week, Stockholm, Sweden, 25-31 August 1991.

19. Mozingo DW, Missavage AE, McManus WF, Pruitt BA Jr: Acalculous cholecystitis diagnosed by Indium –III labeled leukocyte scanning in a severely burned patient. 39th Annual Meeting of the Southwest Surgical Congress, Coronado, California, 16-29 April 1987.

INVITED PRESENTATIONS

1. New Technologies and Burns. Florida Surgical Society 2004 Annual Meeting, Key West, Florida, 25-27 June 2004.

2. Initial Burn Care. Holmes Regional Medical Center, 4 June 2004.

3. Funding for Burn Disaster Preparedness. 36th Annual Meeting of the American Burn Association, Vancouver, British Columbia, 25 March 2004.

4. Advances in Burn Care. Alachua County Medical Society, Gainesville, FL, 9 March 2004.

5. Burn Injury. Anatomy Grand Rounds Fall 03 for 1st year medical students, University of Florida, Gainesville, FL, 29 August 2003.

6. Regulating Healing: From Burns to Chronic Wounds. Wound Healing Symposium, University of Florida, Gainesville, Florida, 23 July 2003.

7. Burn Care for the Unburned. Grand Rounds, Temple University, Department of Surgery, Philadelphia, Pennsylvania, 14 May 2003.

8. The Resident Shortage: Latest Strategies. Sunrise Symposium at the 35th Annual Meeting of the American Burn Association, Miami Beach, Fl, 3 April 2003.

9. Molecular Approaches for Regulating Wound Healing. University of Florida Genetics Institute Seminar, Gainesville, Fl, 04 March 2003.

10. Adrenal Insufficiency in the SICU Setting. University of Florida Continuing Medical Education, Department of Surgery, Gainesville, Fl, January 23, 2003.

11. Updates on Burn Care. Proceedings of the 48th Clinical Meeting of the Frederick A. Coller Surgical Society, Sea Island, Ga, 19 October 2002.

12. Comparison of the Biomechanical Properties of Burns Grafted with Conventional Split Thickness Skin vs. Integra™ Artificial Skin. Proceedings of the 11th Quadrennial Congress of the International Society for Burn Injuries, Seattle, Washington, 11-16 August 2002.

13. The Effect of Silver-Coated Antimicrobial Dressings on Matrix Metalloprotease (MMP) Levels in Lower Extremity Venous Stasis Ulcers, Smith & Nephew Advanced Wound Care Exhibit Symposium, Chicago, Illinois, American Burn Association Annual Meeting, 26 April 2002.

14. Comparison of the Biomedical Properties of Burns Grafted with Conventional Split-thickness Graft vs. Integra®, American Burn Association Satellite Symposium, Chicago, Illinois, 25 April 2002.

15. Burn Center Verification, Sunrise Symposia. Proceedings of the American Burn Association 34th Annual Meeting, Chicago, Illinois, 25 April 2002.

16. Burns in the Very Obese, Educational Symposium, American Burn Association 34th Annual Meeting, Chicago, Illinois, 24 April 2002.

17. Improved Functional Outcome of Skin Grafting for Major Burns Using Dermal Regeneration Technology, Edward M. Copeland III, MD Scientific Symposium, 1 March 2002.

18. Initial Management of Burns, University of Florida Trauma Lecture Series, Gainesville, Florida, 17 January 2002.

19. Burn Resuscitation, Critical Care & Emergency Medicine 2001, Lake Buena Vista, Florida, 21 November, 2001.

20. Wound Bed Preparation, Smith & Nephew Conference, Atlanta, Georgia, 8 November, 2001.

21. Quemaduras Eléctricas (Electrical Injury), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 14 June 2001.

22. Nutrición del Paciente Quemado (Nutrition in Burn Patients), 9 Congeso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 13 June 2001.

23. Tecnología de Reemplazo Dérmico (Dermal Regeneration Technology), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 12 June 2001.

24. Lesión inhalatoria (Inhalation Injury), 9 Congreso Argentino de Quemaduras 2001, Buenos Aires, Argentina, 12 June 2001.

25. Síndrome de necrosis epidermica toxica (Toxic Epidermal Necrolysis Syndrome), 9 Congreso Argentino de Quemadruas 2001, Buenos Aires, Argentina, 11 June 2001.

26. Caring for Burns in the Outpatient Setting, The 14th Annual Symposium on Advanced Wound Care & Medical Research Forum on Wound Repair, Las Vegas, Nevada, 1 May 2001.

27. Wound Bed Preparation, Smith & Nephew Conference, Jacksonville, FL 22 May 2001.

28. Burn Care for the UnBurned, Surgical Grand Round, Cook County Hospital, Chicago, IL, 17 May 2001.

29. Wound Bed Preparation, Smith & Nephew Conference, Chicago, IL, 17 May 2001.

30. Treating Inhalation Injuries, Sunrise Symposium breakfast session, 2001 American Burn Association Meeting, Boston, MA, 19 April 2001.

31. Burn Rehabilitation, Rehab 2001: From Discovery to Recovery, Gainesville, Florida, 11 April 2001.

32. Wound Bed Preparation, Smith & Nephew Wound Conference, Atlanta, GA, 14 December 2000.

33. What's New In Burn Management, Trauma Multidisciplinary Conference, Holmes Regional Medical Center, 7 September 2000.

34. What's New In Burn Management, General Staff CME Conference, Holmes Regional Medical Center, 8 September 2000.

35. Burns, Surgical Basic Science Conference, University of Florida College of Medicine, Gainesville, FL, 6 July 2000.

36. What's New In Burn Management, 2000 Joint Annual Meeting Florida Chapter and South Florida Chapter American College of Surgeons, Palm Beach, FL, 24 June 2000.

37. Thermal Injury, Union County EMS, Lake Butler, FL, 21 June 2000.

38. ATLS Provider Course, University of Florida, Jacksonville, FL, 14 April 2000.

39. Chemical Burns, 32nd Annual Meeting American Burn Association, Las Vegas, NV, 14 March 2000. Thermal Injury, University of Florida Tissue Bank, Gainesville, FL, 29 March 2000.

40. Electric Injury, Putnam Power Plant, Palatka, Florida, 23 March 2000.

41. Electric Injury, Florida Power and Light Seminar, Lake City, Florida, 9 February 2000.

42. Electric Injury, Florida Power and Light Seminar, Palatka, Florida, 16 February 2000.

43. Electric Injury, Florida Power and Light Seminar, St. Augustine, Florida, 23 February 2000.

44. Electric Injury, Florida Power and Light Seminar, St. Johns Service Center, Palatka, Florida, 23 February 2000.

45. Severe Soft Tissue Infection Requiring ICU Care, Critical Care and Emergency Medicine 1999, Lake Buena Vista, FL, 24 November 1999.

46. Diagnostico y tratamiento de la lesion inhalatoria (Diagnosis and Treatment of Inhalation Injury), III Congreso Latinoamericano de Quemaduras, VII Congreso Venezolano de Quemaduras, Puerto La Cruz, Venezuela, 19-23 October 1999.

47. Quemaduras (Burns), VII Congreso Venezolano de Quemaduras, Puerto La Cruz – Venezuela, 19-23 October 1999.

48. ATLS Provider Course. University of Florida, Gainesville, FL, 9 September 1999.

49. New Treatments for Burn Wounds. 2nd Annual Wound Care Symposium. Gainesville, FL, 19 April 1999.

50. Innovations in Wound Care. 31st Annual Meeting American Burn Association, Orlando, FL, 25 March 1999.

51. Faculty, ABLS Instructor Course. 31st Annual Meeting American Burn Association, Orlando, FL, 24 March 1999.

52. Initial Assessment of Burn Injured Patients. ABLS Provider Course, Gainesville, FL, 3 December 1998.

53. Nutritional Support for Severely Burned Patients: XI Congreso Panamericano del Trauma, III Congreso Argentino de Trauma, Buenos Aires, Argentina, 12 November 1998.

54. Geriatric Patients with Deep and Extensive Burns: Early Escharectomy? XI Congreso Panamericano de Trauma, III Congreso Argentinode Trauma, Buenos Aires, Argentian, 12 November 1998. Burns.

55. Fluid Resuscitation of Burn Injury. ABLS provider course. Richmond, VA, 10 October 1998. Initial Burn Management. Doctors' Memorial Hospital. Perry, FL, 1 October 1998.

56. Biomedical Applications in Burn Therapy. University of Florida Biomedical Engineering Course, Gainesville, FL, 6 October 1998.

57. Advanced Trauma Life Support Course. Jacksonville, FL, 16-17 July 1998.

58. Treatment After Inhalation of Toxic Substances, Critical Care & Emergency Medicine 1998, Lake Buena Vista, FL, 21-15 November 1998.

59. Current Burn Care. Grand Rounds, University of Florida Rehabilitation Services, Gainesville, FL, 10 March 1998.

60. Burn Wounds in the Community. First Annual Wound Care Symposium, Gainesville, FL, 2 February 1998.

61. Burn Center Care and Organization. The Rotary Club of Gainesville, Sunrise. Gainesville, FL, 19 February 1998.

62. Burn Care Strategies. Critical Care Update Seminar, Orlando, FL, 25 November 1997.

63. Post-op Trauma Problems. Critical Care Update Seminar, Orlando, FL, 25 November 1997.

64. Perioperative antibiotics in burn surgery. U.S. Army Institute of Surgical Research, 50th Anniversary Symposium, San Antonio, TX, 30 October-2 November 1997.

65. Management of Penetrating Trauma. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.

66. Initial Management of Blunt Trauma. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.

67. Electric Injury. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.

68. Thermal Injury. Burn and Critical Care Symposium, Managua, Nicaragua, 13-15 October 1997.

69. Injuries Due to Burns and Cold. Advanced Trauma Life Support Course. Jacksonville, FL, September 12 1997.

70. Determinants of the Hypermetabolic Response. 37th World Congess of Surgery, International Surgical Week 97, Acapulco, Mexico, 24-20 August 1997.

71. Manejo del Dolor en el Paciente Quemado (Pain Management in Burned Patients). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.

72. Manejo Quirúrgico del Quemado (Surgical Management of Burns). VI Congreso Venezolano de Quemaduras. Ciudad Bolivar, Venezuela, 24-26 July 1997.

73. Papel de la Excisión Temprana del Tejido Quemado Efecto en la Sobrevida (Early Excision of Burns and Effect on Survival), VI Congreso Venezolano de Quemaduras. Ciudad Bolivar, Venezuela, 24-26 July 1997.

74. Manejo de la Fase Aguda del Quemado (Fluid Resuscitation in Burn Patients. VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.

75. Antimicrobianos de uso Tópico, Futuro y Resistencia Bacteriana (The Use of Topical Antimicrobial Agents and Development of Resistant Bacteria). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.

76. Lesión Inhalatoria y Manejo Crítico (Inhalation Injury and Critical Care Management). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.

77. Manejo de la Fase Aguda de las Quemaduras in Ninos (Fluid Resuscitation in Pediatric Burn Patients). VI Congreso Venezolano de Quemaduras, Ciudad Bolivar, Venezuela, 24-26 July 1997.

78. Smoke Inhalation Injury: Diagnosis and Treatment. Surgical Grand Rounds, University of Florida, Department of Surgery, Gainesville, FL, 9 April 1997.

79. New Techniques of Mechanical Ventilation. Sunrise Symposium at the 29th Annual Meeting of the American Burn Association, New York, NY, 22 March

1997.

80. Thrombosis Prophylaxis: Should we be filtering or anticoagulating our patients? The 29th Annual Meeting of the American Burn Association, New York, NY, 21 March 1997.

81. Practical Pulmonary Physiology. University of North Dakota, Surgical Residents Seminar, Grand Forks, ND, 29 January 1997.

82. Burn Wound Closure: A Search for the Holy Grail. Medical Staff Grand Rounds, University of North Dakota, Grand Forks, ND, 29 January 1997.

83. Burn Center Verification 9th Annual Regional Burn Seminar, Charleston, SC, 6-8 December 1996.

84. Toxic Epidermal Necrolysis Syndrome, University of Florida Department of Surgery Grand Rounds, Gainesville, FL, 4 December 1996.

85. Difficult Surgical Problems. Critical Care Update Seminar, Orlando, FL, 25-26 November 1996.

86. Initial Trauma Care. Critical Care Update Seminar, Orlando, FL 25-26 November 1996.

87. Resuscitation of the Burn Patient, University of Florida, Critical Care Update Seminar, Orlando, FL, 25-26 November 1996.

88. Ethical Decision Making in Burn Care. First Annual San Antonio Trauma Symposium, San Antonio, TX, 16-17 September 1996.

89. Progress in Burn Care, University of Florida, Department of Surgery Grand Rounds, Gainesville, FL, 25 September 1996.

90. Cost Effectiveness of Cultured Epidermal Autografts in Burn Patients. Annual Meeting of the Wound Healing Society, Boston, MA, 16-19 May 1996.

91. Pulmonary Assessment of the Burned Patient. 28th Annual Meeting of the American Burn Association, Nashville, TN, 7-10 March 1996.

92. The Burn Patient with Co-morbid Factors. 28th Annual Meeting of the American Burn Association, Nashville, TN, 7-10 March 1996.

93. Mission of the U.S. Army Institute of Surgical Research, Alamo Federal Executive Board Leadership Course, Fort Sam Houston, TX, 10 January 1996.

PDR®

54

EDITION

2000

PHYSICIANS' DESK REFERENCE®

Senior Vice President, Directory Services: Paul Walsh

Director of Product Management: Mark A. Friedman
Associate Product Manager: Bill Shaughnessy
Senior Business Manager: Mark S. Ritchin
Financial Analyst: Wayne M. Soltis
Director of Sales: Dikran N. Barsamian
National Sales Manager, Pharmaceutical Sales: Anthony Sorce
National Account Manager: Don Bruccoleri
Senior Account Manager: Frank Karkowsky
Account Managers:
Marion Gray, RPh
Lawrence C. Keary
Jeffrey F. Pfohl
Suzanne E. Yarrow, RN
Electronic Sales Account Manager: Stephen M. Silverberg
National Sales Manager, Medical Economics Trade Sales: Bill Gaffney
Director of Direct Marketing: Michael Bennett
List and Production Manager: Lorraine M. Loening
Senior Marketing Analyst: Dina A. Maeder

Director, New Business Development and Professional Support Services: Mukesh Mehta, RPh
Manager, Drug Information Services: Thomas Fleming, RPh
Drug Information Specialist: Maria Deutsch, MS, RPh, CDE
Editor, Directory Services: David W. Sifton
Senior Associate Editor: Lori Murray
Director of Production: Carrie Williams
Manager of Production: Kimberly H. Vivas
Senior Production Coordinator: Amy B. Brooks
Production Coordinators: Gianna Caradonna, Maria Volpati
Data Manager: Jeffrey D. Schaefer
Senior Format Editor: Gregory J. Westley
Index Editors: Johanna M. Mazur, Robert N. Woerner
Art Associate: Joan K. Akerlind
Senior Digital Imaging Coordinator: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Electronic Publishing Designer: Livio Udina
Fulfillment Manager: Stephanie DeNardi

Officers of Medical Economics Company: *President and Chief Executive Officer:* Curtis B. Allen; *Vice President, New Media:* L. Suzanne BeDell; *Vice President, Corporate Human Resources:* Pamela M. Bilash; *Vice President and Chief Information Officer:* Steven M. Bressler; *Chief Financial Officer:* Christopher Caridi; *Vice President and Controller:* Barry Gray; *Vice President, New Business Planning:* Linda G. Hope; *Vice President, Business Integration:* David A. Pitler; *Vice President, Finance:* Donna Santarpia; *Senior Vice President, Directory Services:* Paul Walsh; *Senior Vice President, Operations:* John R. Ware; *Senior Vice President, Internet Strategies:* Raymond Zoëller

Printed on recycled paper

ISBN: 1-56363-330-2

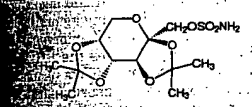
maceutical, McNEIL-AB, Inc.
PA 19477
1997 643-10-089-2
Product Identification Guide, page 329

℞

X®
capsules)
sules

TION

a sulfamate-substituted monosaccharide that
ous as an antiepileptic drug. TOPAMAX®
capsules) Sprinkle Capsules are available as 15
g sprinkle capsules for oral administration as
les or for opening and sprinkling onto soft food.
a white crystalline powder with a bitter taste.
most soluble in alkaline solutions containing
ride or sodium phosphate and having a pH of
freely soluble in acetone, chloroform, dimeth-
and ethanol. The solubility in water is 9.8 mg/
rated solution has a pH of 6.3. Topiramate has
ar formula $C_{12}H_{21}NO_8S$ and a molecular weight
piramate is designated chemically as 2,3:4,5-
ylidene-β-D-fructopyranose sulfamate and has
structural formula:



topiramate capsules) Sprinkle Capsules con-
ntercoated beads in a hard gelatin capsule. The
redients are: sugar spheres (sucrose and starch),
ulose acetate, gelatin, silicone dioxide, sodium
titanium dioxide, and black pharmaceutical

PHARMACOLOGY

n of Action:
mechanism by which topiramate exerts its an-
ures is unknown; however, electrophysiological
linical studies of the effects of topiramate on cul-
ons have revealed three properties that may con-
piramate's antiepileptic efficacy. First, action
ials elicited repetitively by a sustained depolarization
ons are blocked by topiramate in a time-depen-
ner suggestive of a state-dependent sodium chan-
ation. Second, topiramate increases the fre-
which γ-aminobutyrate (GABA) activates $GABA_A$
and enhances the ability of GABA to induce a flux
ons into neurons, suggesting that topiramate
s the activity of this inhibitory neurotransmitter.
was not blocked by flumazenil, a benzodiazepine
nor did topiramate increase the duration of the
ons, differentiating topiramate from barbitu-
modulate $GABA_A$ receptors. Third, topiramate
the ability of kainate to activate the kainate/
amino-3-hydroxy-5-methylisoxazole-4-propionic
(AMPA) subtype of excitatory amino acid (gluta-
ion, but has no apparent effect on the activity of
spartate (NMDA) at the NMDA receptor sub-
effects of topiramate are concentration-depen-
the range of 1 μM to 200 μM.
also inhibits some isoenzymes of carbonic anhy-
(CA-II and CA-IV). This pharmacologic effect is gen-
weaker than that of acetazolamide, a known carbonic
inhibitor, and is not thought to be a major con-
tor to topiramate's antiepileptic activity.
namics:
has anticonvulsant activity in rat and mouse
ximal shock seizure (MES) tests. Topiramate is
ctive in blocking clonic seizures induced by
receptor antagonist, pentylenetetrazole.
is also effective in rodent models of epilepsy,
ding tonic and absence-like seizures in the spon-
leptic rat (SER) and tonic and clonic seizures in-
ed by kindling of the amygdala or by global is-
netics:
formulation is bioequivalent to the immediate
formulation and, therefore, may be substi-
herapeutic equivalent.
piramate is rapid, with peak plasma concen-
ing at approximately 2 hours following a 400
the relative bioavailability of topiramate from
mulation is about 80% compared to a solution.
ability of topiramate is not affected by food.
okinetics of topiramate are linear with dose
increases in plasma concentration over the
udied (200 to 800 mg/day). The mean plasma
alf-life is 21 hours after single or multiple
state is thus reached in about 4 days in pa-
ormal renal function. Topiramate is 13–17%
man plasma proteins over the concentration
mg/mL.

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Dose Stabilization	Placebo[a]	Target Topiramate Dosage (mg/day) 200	400	600	800	1,000
YD	N	42	42	40	41	—	—
	Mean Dose	5.9	200	390	556	—	—
	Median Dose	6.0	200	400	600	—	—
YE	N	44	—	—	40	45	40
	Mean Dose	9.7	—	—	544	739	796
	Median Dose	10.0	—	—	600	800	1,000
Y1	N	23	—	19	—	—	—
	Mean Dose	3.8	—	395	—	—	—
	Median Dose	4.0	—	400	—	—	—
Y2	N	30	—	—	28	—	—
	Mean Dose	5.7	—	—	522	—	—
	Median Dose	6.0	—	—	600	—	—
Y3	N	28	—	—	—	25	—
	Mean Dose	7.9	—	—	—	568	—
	Median Dose	8.0	—	—	—	600	—

[a] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocol YD and Y2, 6 tablets/day; Protocol Y3, 8 tablets/day; YE, 10 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

Protocol	Efficacy results	Placebo	Target Topiramate Dosage (mg/day) 200	400	600	800	1,000
YD	N	45	45	45	46	—	—
	Mean % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	—	—
	% Responders	18	24	44[d]	46[d]		
YE	N	47	—	—	48	48	47
	Median % Reduction	1.7	—	—	40.8[c]	41.0[c]	36.0[c]
	% Responders	9	—	—	40[c]	41[c]	36[d]
Y1	N	24	—	23	—	—	—
	Median % Reduction	1.1	—	40.7[a]	—	—	—
	% Responders	8	—	35[d]	—	—	—
Y2	N	30	—	—	30	—	—
	Median % Reduction	-12.2	—	—	46.4[f]	—	—
	% Responders	10	—	—	47[c]	—	—
Y3	N	28	—	—	—	28	—
	Median % Reduction	-20.6	—	—	—	24.3[c]	—
	% Responders	0	—	—	—	43[c]	—

Comparisons with placebo; [a]$p = 0.080$; [b]$p \leq 0.010$; [c]$p \leq 0.001$; [d]$p \leq 0.050$; [e]$p = 0.065$; [f]$p \leq 0.005$.

lation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Pharmacokinetic Interaction (see also Drug Interactions):
Antiepileptic Drugs
Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized under **PRECAUTIONS (Table 3).**

Special Populations:
Renal Impairment:
The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30–69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual dose is recommended in patients with moderate or severe renal impairment.

Hemodialysis:
Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialy-

Age, Gender, and Race:
Clearance of topiramate was not affected by age (18–67 years), gender, or race.

Pediatric Pharmacokinetics:
Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose. Although the relationship between age and clearance among patients of pediatric age has not been systematically evaluated, it appears that the weight adjusted clearance of topiramate is 50% higher in pediatric patients than in adults.

CLINICAL STUDIES

The studies described in the following section were conducted using TOPAMAX® (topiramate) Tablets.

The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and three comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8–12 week baseline phase. Patients who experienced at least 12 (or 8, for 8-week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® Tablets in addition to their other AEDs. Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or

Topamax—Cont.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2.

[See table 2 on previous page]

Subset analyses of the antiepileptic efficacy of TOPAMAX® Tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate capsules) Sprinkle Capsules are indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate capsules) Sprinkle Capsules are contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

Withdrawal of AEDs

Antiepileptic drugs, including TOPAMAX®, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Congnitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX® were central nervous system-related. The most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials (see **ADVERSE REACTIONS, Table 5**).

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at dosages above 400 mg/day.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate) Tablets, 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).

This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX® (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX® program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS

General:

Kidney Stones

A total of 32/2,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2–4 times that expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see **DOSAGE AND ADMINISTRATION**).

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation (see **PRECAUTIONS: General**, for support regarding hydration as a preventative measure).

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Please refer to the end of the product labeling for important information on how to take TOPAMAX® (topiramate capsules) Sprinkle Capsules.

Drug Interactions:

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

[a] = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

[b] = Is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cogintive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In a pharmacokinetic interaction study with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX® did not significantly affect the clearance of norethindrone. The mean oral clearance of ethinyl estradiol at 800 mg/day dose was increased by 47% (range: 13–107%). The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300 mg/kg, was primarily due to the increased occurrence of a smooth muscle tumor considered histomorphologically unique to mice. Plasma exposures in mice receiving 300 mg/kg were approximately 0.5 to 1 times steady state exposures measured in patients receiving topiramate monotherapy at the recommended human dose (RHD) of 400 mg, and 1.5 to 2 times steady state topiramate exposures in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is uncertain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg (approximately 3 times the RHD on a

lymphoma assay; it did not increase unscheduled [illegible] thesis in rat hepatocytes *in vitro*; and it did [illegible] chromosomal aberrations in human lymphocytes [illegible] in rat bone marrow *in vivo*.

No adverse effects on male or female fertility were [illegible] in rats at doses up to 100 mg/kg (2.5 times the RHD [illegible] mg/m^2 basis).

Pregnancy: Pregnancy Category C.

Topiramate has demonstrated selective developmental [illegible] icity, including teratogenicity, in experimental animal [illegible] ies. When oral doses of 20, 100, or 500 mg/kg were [illegible] istered to pregnant mice during the period of organogenesis, the incidence of fetal malformations (primarily craniofacial defects) was increased at all doses. The low dose is approximately 0.2 times the recommended human dose (RHD) of 400 mg/day) on a mg/m^2 basis. Fetal body weights and skeletal ossification were reduced at 500 mg/kg in conjunction with decreased maternal body weight gain.

In rat studies (oral doses of 20, 100, and 500 mg/kg [illegible] 2.5, 30 and 400 mg/kg), the frequency of limb malformations (ectrodactyly, micromelia, and amelia) was increased among the offspring of dams treated with 400 mg/kg (10 times the RHD on a mg/m^2 basis) or greater during the organogenesis period of pregnancy. Embryotoxicity (reduced fetal body weights, increased incidence of structural variations) was observed at doses as low as 20 mg/kg (0.5 times the RHD on a mg/m^2 basis). Clinical signs of maternal toxicity were seen at 400 mg/kg and above, and maternal body weight gain was reduced during treatment with 100 mg/kg or greater.

In rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 150 mg/kg orally during organogenesis), embryo/fetal mortality was increased at 35 mg/kg (2 times the RHD on a mg/m^2 basis) or greater, and teratogenic effects (primarily rib and vertebral malformations) were observed at 120 mg/kg (6 times the RHD on a mg/m^2 basis). Evidence of maternal toxicity (decreased body weight gain, clinical signs, and/or mortality) was seen at 35 mg/kg and above. When females [illegible] were treated during the latter part of gestation and throughout lactation (0.2, 4, 20, and 100 mg/kg or 2, 20, and 200 mg/kg), offspring exhibited decreased viability and delayed physical development at 200 mg/kg (5 times the RHD on a mg/m^2 basis) and reductions in pre- and/or postweaning body weight gain at 2 mg/kg (0.05 times the RHD on a mg/m^2 basis) and above.

Maternal toxicity (decreased body weight gain, clinical signs) was evident at 100 mg/kg or greater.

In a rat embryo/fetal development study with a postnatal component (0.2, 2.5, 30 or 400 mg/kg during organogenesis noted above), pups exhibited delayed physical development at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and persistent reductions in body weight gain at 30 mg/kg (1 time the RHD on a mg/m^2 basis) and higher.

There are no studies using TOPAMAX® in pregnant women. TOPAMAX® should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

Labor and Delivery:

In studies of rats where dams were allowed to deliver pups naturally, no drug-related effects on gestation length or parturition were observed at dosage levels up to 200 mg/kg/day. The effect of TOPAMAX® on labor and delivery in humans is unknown.

Nursing Mothers:

Topiramate is excreted in the milk of lactating rats. It is not known if topiramate is excreted in human milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX® is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendations regarding nursing.

Pediatric Use:

Safety and effectiveness in children have not been established. The pharmacokinetic profile of TOPAMAX® was studied in patients between the ages of 4 and 17 years (see **CLINICAL PHARMACOLOGY; Pediatric Pharmacokinetics**).

Geriatric Use:

In clinical trials, 2% of patients were over 60. No age related difference in effectiveness or adverse effects were seen. There were no pharmacokinetic differences related to age alone, although the possibility of age-associated renal functional abnormalities should be considered.

Race and Gender Effects:

Evaluation of efficacy and safety in clinical trials has shown no race or gender related effects.

ADVERSE REACTIONS

The data described in the following section were obtained using TOPAMAX® (topiramate) Tablets.

The most commonly observed adverse events associated with the use of topiramate at dosages of 200 to 400 mg/day in controlled trials, that were seen at greater frequency in topiramate-treated patients and did not appear to be dose related were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing,

...blems, anxiety, mood problems, cognitive prob-
...otherwise specified, weight decreased, and tremor
...e 5).
...lled clinical trials, 11% of patients receiving topi-
...200 to 400 mg/day as adjunctive therapy discontin-
...to adverse events. This rate appeared to increase at
...above 400 mg/day. Adverse events associated with
...ning therapy included somnolence, dizziness, anxi-
...ficulty with concentration or attention, fatigue, and
...esia and increased at dosages above 400 mg/day.
...mately 28% of the 1,715 indiviuals with epilepsy
...received topiramate at dosages of 200 to 1,600 mg/day
...linical studies discontinued treatment because of ad-
...vents; an individual patient could have reported
...than one adverse event.
...adverse events were: psychomotor slowing (4.1%), dif-
...with memory (3.3%), fatigue (3.3%), confusion (3.2%),
...ence (3.2%), difficulty with concentration/attention
...anorexia (2.9%), depression (2.6%), dizziness (2.6%),
...decrease (2.5%), nervousness (2.2%), ataxia (2.2%),
...esthesia (2.0%), and language problems (2.0%).

...ence in Controlled Clinical Trials—Add-On Therapy

...lists treatment-emergent adverse events that oc-
...in at least 1% of patients treated with 200 to 400
...topiramate in controlled trials that were numeri-
...more common at this dose than in the patients treated
...placebo. In general, most patients who experienced ad-
...events during the first eight weeks of these trials no
...experienced them by their last visit.
...prescriber should be aware that these data were ob-
...when TOPAMAX® was added to concurrent antiepi-
...drug therapy and cannot be used to predict the fre-
...of adverse events in the course of usual medical
...where patient characteristics and other factors may
...from those prevailing during clinical studies. Simi-
...the cited frequencies cannot be directly compared with
...obtained from other clinical investigations involving
...treatments, uses, or investigators. Inspection of
...frequencies, however, does provide the prescribing
...with a basis to estimate the relative contribution
...and non-drug factors to the adverse event incidences
...population studied.
...[Table 4 above]
...[Table 5 at top of next page]

...Adverse Events Observed

...events that occurred in more than 1% of patients
...with 200 to 400 mg of topiramate in placebo-con-
...trials but with equal or greater frequency in the pla-
...group were: fatigue, headache, injury, anxiety, rash,
...convulsions aggravated, coughing, gastroenteritis, rhi-
...back pain, hot flushes, bronchitis, abnormal gait, in-
...voluntary muscle contractions, and epistaxis.

...Adverse Events Observed During All Clinical Trials

...ramate, initiated as adjunctive therapy, has been ad-
...istered to 1,715 patients with epilepsy during all clinical
...s. During these studies, all adverse events were re-
...ded by the clinical investigators using terminology of
...own choosing. To provide a meaningful estimate of the
...portion of individuals having adverse events, similar
...of events were grouped into a smaller number of stan-
...dized categories using modified WHOART dictionary
...nology. The frequencies presented represent the pro-
...tion of 1,715 topiramate-treated patients who experi-
...an event of the type cited on at least one occasion
...receiving topiramate. Reported events are included
...those already listed in the previous table, those too
...l to be informative, and those not reasonably associ-
...with the use of the drug.
...are classified within body system categories and
...ated in order of decreasing frequency using the fol-
...definitions: *frequent* occurring in at least 1/100 pa-
...*infrequent* occurring in 1/100 to 1/1000 patients; *rare*
...ring in fewer than 1/1000 patients.

...**Nervous System Disorders:** *Infrequent:* vaso-
...

...**as a Whole:** *Frequent:* fatigue, fever, malaise. *Infre-*
...syncope, halitosis, abdomen enlarged. *Rare:* alcohol
...ance, substernal chest pain, sudden death.

...**vascular Disorders, General:** *Infrequent:* hyperten-
...hypotension, postural hypotension.

...**& Peripheral Nervous System Disorders:** *Fre-*
...hypokinesia, vertigo, stupor, convulsions grand mal,
...tonesia, hypertonia. *Infrequent:* leg cramps, hypore-
...neuropathy, migraine, apraxia, hyperaesthesia, dys-
...hyperreflexia, dysphonia, scotoma, ptosis, dystonia,
...field defect, coma, encephalopathy, fecal inconti-
...upper motor neuron lesion. *Rare:* cerebellar syn-
...EEG abnormal, tongue paralysis.

...**Disorders:** *Infrequent:* goiter. *Rare:* thyroid dis-
...

...**testinal System Disorders:** *Frequent:* diarrhea,
...flatulence, gastroenteritis. *Infrequent:* gum hyper-
...hemorrhoids, tooth caries, stomatitis, dysphagia,
...gastritis, saliva increased, hiccough, gastroesopha-
...tongue edema, esophagitis. *Rare:* eructation.

...**and Vestibular Disorders:** *Frequent:* tinnitus.
...ache, hyperacusis.

...**and Rhythm Disorders:** *Frequent:* palpitation.
...AV block, bradycardia, bundle branch block.
...hythmia, arrhythmia atrial, fibrillation atrial.

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials[a,b]
(Events that occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event[c]	TOPAMAX® Dosage (mg/day) Placebo (N=174)	200–400 (N=113)	600–1,000 (N=247)
Body as a Whole - General Disorders			
Asthenia	1.1	8.0	4.5
Back Pain	4.0	6.2	2.0
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	3.2
Leg Pain	2.3	3.5	2.4
Hot Flushes	1.7	2.7	0.8
Body Odor	0.0	1.8	0.0
Edema	1.1	1.8	1.2
Rigors	0.0	1.8	0.4
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.4
Ataxia	6.9	21.2	17.0
Speech Disorders/ Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.6
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoaesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female	(N=39)	(N=24)	(N=42)
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.5
Eye Pain	1.1	1.8	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

Topamax—Cont.

tase increased, dehydration, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, creatinine increased, hyperchloremia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypocholesterolemia, hypoglycemia, hypophosphatemia.
Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.
Myo-, Endo-, Pericardial & Valve Disorders: *Infrequent:* angina pectoris.
Neoplasms: *Infrequent:* basal cell carcinoma, thrombocythemia. *Rare:* polycythemia.
Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, purpura, thrombocytopenia, pulmonary embolism.
Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.
Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.
Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.
Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.
Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngismus.
Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhoea, sweating decreased, abnormal hair texture. *Rare:* chloasma.
Special Senses Other, Disorders: *Frequent:* taste perversion. *Infrequent:* taste loss, parosmia.
Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.
Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.
Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.
White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdosage is not recommended. Treatment should be appropriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve responses.
The recommended total daily dose of TOPAMAX® (topiramate capsules) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.
The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®.

Table 5: Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	Placebo (N=174)	TOPAMAX® Dosage (mg/day) 200 (N=45)	400 (N=68)
Fatigue	14.4	11.1	11.8
Nervousness	7.5	13.3	17.6
Difficulty with Concentration/Attention	1.1	6.7	8.8
Confusion	5.2	8.9	10.3
Depression	6.3	8.9	7.4
Anorexia	4.0	4.4	5.9
Language problems	0.6	2.2	8.8
Anxiety	5.2	2.2	2.9
Mood problems	1.7	0.0	5.9
Cognitive problems NOS	0.6	0.0	0.0
Weight decrease	2.3	4.4	8.8
Tremor	6.3	13.3	8.8

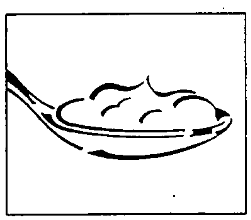
small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.
Patients with Renal Impairment:
In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m²), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.
Patients Undergoing Hemodialysis:
Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.
Patients with Hepatic Disease:
In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

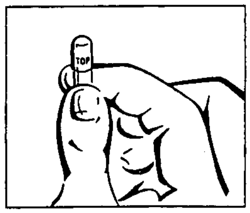
TOPAMAX® (topiramate capsules) Sprinkle Capsules contain small, white to off-white spheres. The gelatin capsules are white and clear.
They are marked as follows:
15 mg capsules with "TOP" and "15 mg" on the side.
25 mg capsules with "TOP" and "25 mg" on the side.
The capsules are supplied as follows:
15 mg capsules bottles of 60 (NDC 0045-0647-65)
25 mg capsules bottles of 60 (NDC 0045-0645-65)
TOPAMAX® (topiramate capsules) Sprinkle Capsules should be stored in tightly-closed containers at or below 25° C (77°F). Protect from moisture.
TOPAMAX® (topiramate capsules) is a trademark of OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC.

HOW TO TAKE TOPAMAX® (topiramate capsules) SPRINKLE CAPSULES

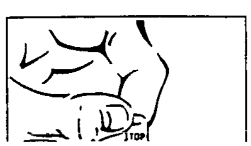
A Guide for Patients and Their Caregivers
Your doctor has given you a prescription for TOPAMAX® (topiramate capsules) Sprinkle Capsules. Here are your instructions for taking this medication. Please read these instructions prior to use.



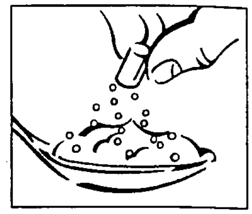
To Take With Food
You may sprinkle the contents of TOPAMAX® Sprinkle Capsules on a small amount (teaspoon) of soft food, such as applesauce, custard, ice cream, oatmeal, pudding, or yogurt.



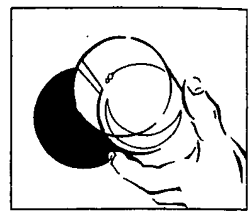
Hold the capsule upright so that you can read the word "TOP".



Carefully twist off the clear portion of the capsule. You may find it best to do this over the small portion of the food onto which you will be pouring the



Sprinkle all of the ... sule's contents ... spoonful of soft ... taking care to ... the entire ... dosage ... onto the food ...



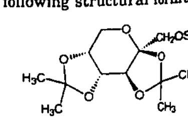
Be sure the ... swallows the ... spoonful of the ... kle/food mixture ... diately. ... should be avoided ... may be helpful to ... the patient drink ... immediately in order ... make sure all of the ... mixture is swallowed. IMPORTANT: ... store any sprinkle ... mixture for use ... later time.

To Take Without Food
TOPAMAX® Sprinkle Capsules may also be swallowed ... whole capsules.
For more information about TOPAMAX® Sprinkle Capsules, ask your doctor or pharmacist.
OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, NJ 08869
 Issued February 1999 ... 643-10-...
Shown in Product Identification Guide, page 329

TOPAMAX®
[*tō′-pă-măx*]
(topiramate) tablets

DESCRIPTION

TOPAMAX® (topiramate) is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic drug. It is available as 25 mg, 100 mg, and 200 mg round tablets for oral administration.
Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.36. Topiramate is designated chemically as 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX® (topiramate) Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide (100 and 200 mg tablets) and polysorbate 80.

CLINICAL PHARMACOLOGY

Mechanism of Action:
The precise mechanism by which topiramate exerts its antiseizure effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on cultured neurons have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, ... sustained de...

enhances the ability of GABA to induce a flux ions into neurons, suggesting that topiramate his activity of this inhibitory neurotransmitter. not blocked by flumazenil, a benzodiazepine or did topiramate increase the duration of the time, differentiating topiramate from barbitu- modulate $GABA_A$ receptors. Third, topiramate the ability of kainate to activate the kainate/ amino-3-hydroxy-5-methylisoxazole-4-propionic (AMPA) subtype of excitatory amino acid (gluta- but has no apparent effect on the activity of -aspartate (NMDA) at the NMDA receptor sub- effects of topiramate are concentration-depen- the range of 1 µM to 200 µM.

also inhibits some isoenzymes of carbonic anhy- rase (CA-IV). This pharmacologic effect is gen- than that of acetazolamide, a known carbonic inhibitor, and is not thought to be a major con- tor to topiramate's antiepileptic activity.

namics:

has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is effective in blocking clonic seizures induced by receptor antagonist, pentylenetetrazole. Topira- effective in rodent models of epilepsy, which in- and absence-like seizures in the spontaneous ep- (SER) and tonic and clonic seizures induced in of the amygdala or by global ischemia.

netics:

topiramate is rapid, with peak plasma concen- curring at approximately 2 hours following a 400 the relative bioavailability of topiramate from mulation is about 80% compared to a solution. ability of topiramate is not affected by food. kinetics of topiramate are linear with dose increases in plasma concentration over the studied (200 to 800 mg/day). The mean plasma half-life is 21 hours after single or multiple dose state is thus reached in about 4 days in pa- normal renal function. Topiramate is 13–17% human plasma proteins over the concentration 250 ng/mL.

and Excretion:

is not extensively metabolized and is primarily unchanged in the urine (approximately 70% of ered dose). Six metabolites have been identified none of which constitutes more than 5% of an dose. The metabolites are formed via hydrox- and glucuronidation. There is evidence tubular reabsorption of topiramate. In rats, given inhibit tubular reabsorption, along with topi- significant increase in renal clearance of topira- observed. This interaction has not been evaluated Overall, plasma clearance is approximately 20 in humans following oral administration.

tic Interactions (see also Drug Interactions):

Drug

interactions between topiramate and standard assessed in controlled clinical pharmacokinetic patients with epilepsy. The effect of these inter- on plasma AUCs are summarized under PRE- (Table 3):

ations:

ment:

e of topiramate was reduced by 42% in moder- impaired (creatinine clearance 30–69 mL/min/ by 54% in severely renally impaired subjects clearance <30 mL/min/1.73m^2) compared to nor- function subjects (creatinine clearance >70 mL/ Since topiramate is presumed to undergo sig- tubular reabsorption, it is uncertain whether this can be generalized to all situations of renal im- It is conceivable that some forms of renal disease substantially affect glomerular filtration rate and tub- function resulting in a clearance of topiramate not by creatinine clearance. In general, however, use the usual dose is recommended in patients with severe renal impairment.

is cleared by hemodialysis. Using a high effi- low-flux, single-pass-dialysate hemodialysis pro- topiramate dialysis clearance was 120 mL/min with through the dialyzer at 400 mL/min. This high compared to 20–30 mL/min total oral clearance adults), will remove a clinically significant topiramate from the patient over the hemodialy- period. Therefore, a dose adjustment may be (DOSAGE AND ADMINISTRATION).

ment:

impaired subjects, the clearance of topira- decreased; the mechanism underlying the de- is well understood.

and Race:

topiramate was not affected by age (18–67 or race.

macokinetics:

netics of topiramate were evaluated in patients years receiving one or two other antiepileptic pharmacokinetic profiles were obtained after one

Table 1: Topiramate Dose Summary During the Stabilization Periods of Each of Five Double-Blind, Placebo-Controlled, Add-On Trials

			Target Topiramate Dosage (mg/day)				
Protocol	Stabilization Dose	Placebo[a]	200	400	600	800	1,000
YD	N	42	42	40	41	-	-
	Mean Dose	5.9	200	390	556	-	-
	Median Dose	6.0	200	400	600	-	-
YE	N	44	-	-	40	45	40
	Mean Dose	9.7	-	-	544	739	796
	Median Dose	10.0	-	-	600	800	1,000
Y1	N	23	-	19	-	-	-
	Mean Dose	3.8	-	395	-	-	-
	Median Dose	4.0	-	400	-	-	-
Y2	N	30	-	-	28	-	-
	Mean Dose	5.7	-	-	522	-	-
	Median Dose	6.0	-	-	600	-	-
Y3	N	28	-	-	-	25	-
	Mean Dose	7.9	-	-	-	568	-
	Median Dose	8.0	-	-	-	600	-

[a]Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol Y1, 4 tablets/day; Protocols YD and Y2, 6 tablets/day; Protocol Y3, 8 tablets/day; Protocols YE, 10 tablets/day.

Table 2: Median Percent Seizure Rate Reduction and Percent Responders in Five Double-Blind, Placebo-Controlled, Add-On Trials

			Target Topiramate Dosage (mg/day)				
Protocol	Efficacy Results	Placebo	200	400	600	800	1,000
YD	N	45	45	45	46	-	-
	Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	-	-
	% Responders	18	24	44[d]	46[d]	-	-
YE	N	47	-	-	48	48	47
	Median % Reduction	1.7	-	-	40.8[c]	41.0[c]	36.0[c]
	% Responders	9	-	-	40[c]	41[c]	36[d]
Y1	N	24	-	23	-	-	-
	Median % Reduction	1.1	-	40.7[e]	-	-	-
	% Responders	8	-	35[d]	-	-	-
Y2	N	30	-	-	30	-	-
	Median % Reduction	-12.2	-	-	46.4[f]	-	-
	% Responders	10	-	-	47[c]	-	-
Y3	N	28	-	-	-	28	-
	Median % Reduction	20.6	-	-	-	24.3[c]	-
	% Responders	0	-	-	-	43[c]	-

Comparisons with placebo: [a]p = 0.080, [b] p≤0.010; [c] p≤0.001; [d] p≤0.050; [e]p=0:065; [f] p≤0.005

CLINICAL STUDIES

The effectiveness of topiramate as an adjunctive treatment for partial onset seizures was established in five multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and three comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalization.

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8–12 week baseline phase. Patients who experienced at least 12 (or 8, for 8–week baseline studies) partial onset seizures, with or without secondarily generalization, during the baseline phase were randomly assigned to placebo or a specified dose of TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. After titration, patients entered an 8 or 12–week stabilization period. The numbers of patients randomized to each dose, and the actual mean, and median doses in the stabilization period are shown in Table 1.

[See table 1 above]

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. Responder rate (fraction of patients with at least a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 2.

[See table 2 above]

Subset analyses of the antiepileptic efficacy of TOPAMAX® in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

INDICATIONS AND USAGE

TOPAMAX® (topiramate) is indicated as adjunctive therapy for the treatment of adults with partial onset seizures.

CONTRAINDICATIONS

TOPAMAX® (topiramate) is contraindicated in patients with a history of hypersensitivity to any component of this

Cognitive/Neuropsychiatric Adverse Events

Adverse events most often associated with the use of TOPAMAX® were central nervous system-related. The most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage in the five double-blind trials [see **ADVERSE REACTIONS, Table 5**].

Somnolence and fatigue were the most frequently reported adverse events during clinical trials with TOPAMAX®. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at dosages above 400 mg/day.

Sudden Unexplained Death in Epilepsy (SUDEP)

During the course of premarketing development of TOPAMAX® (topiramate), 10 sudden and unexplained deaths were recorded among a cohort of treated patients (2,796 subject years of exposure).

This represents an incidence of 0.0035 deaths per patient year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving TOPAMAX (ranging from 0.0005 for the general population of patients with epilepsy, to 0.003 for a clinical trial population similar to that in the TOPAMAX program, to 0.005 for patients with refractory epilepsy).

PRECAUTIONS

General:

Kidney Stones

A total of 32/2,086 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney

Topamax—Cont.

An explanation for the association of TOPAMAX® and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of TOPAMAX® with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX®.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required (see **DOSAGE AND ADMINISTRATION**).

Decreased Hepatic Function

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

Information for Patients:

Patients, particularly those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation [see **PRECAUTIONS: General,** for support regarding hydration as a preventative measure].

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Drug Interactions:

Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized in the following table:

In Table 3, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added.

The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when TOPAMAX® was given alone.

Table 3: Summary of AED Interactions with TOPAMAX®

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	NC or 25% increase[a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide[b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

[a] = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.
[b] = is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with oral contraceptives using a combination product containing norethindrone and ethinyl estradiol, TOPAMAX® did not significantly affect the clearance of norethindrone. The mean total exposure to the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400, and 800 mg/day, respectively. Therefore, efficacy of oral contraceptives may be compromised by topiramate. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. The effect of oral contraceptives on the pharmacokinetics of topiramate is not known.

Others: Concomitant use of TOPAMAX®, a weak carbonic

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials[a,b] (Events occurred in at least 1% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

Body System/ Adverse Event[c]	TOPAMAX® Dosage (mg/day) Placebo (N=174)	200-400 (N=113)	600-1,000 (N=247)
Body as a Whole - General Disorders			
Asthenia	1.1	8.0	4.5
Back Pain	4.0	6.2	2.0
Chest Pain	2.3	4.4	2.0
Influenza-Like Symptoms	2.9	3.5	3.2
Leg Pain	2.3	3.5	2.4
Hot Flushes	1.7	2.7	0.8
Body Odor	0.0	1.8	0.0
Edema	1.1	1.8	1.2
Rigors	0.0	1.8	0.4
Central & Peripheral Nervous System Disorders			
Dizziness	14.4	28.3	32.4
Ataxia	6.9	21.2	17.0
Speech Disorders/ Related Speech Problems	2.9	16.8	13.8
Nystagmus	11.5	15.0	15.0
Paresthesia	3.4	15.0	14.6
Tremor	6.3	10.6	13.8
Language Problems	0.6	6.2	11.7
Coordination Abnormal	1.7	5.3	3.6
Hypoaesthesia	1.1	2.7	0.8
Gastrointestinal System Disorders			
Nausea	6.3	11.5	13.8
Dyspepsia	5.2	8.0	5.7
Abdominal Pain	2.9	5.3	7.3
Constipation	0.6	5.3	3.2
Dry Mouth	1.1	2.7	3.2
Gingivitis	0.0	1.8	0.4
Hearing and Vestibular Disorders			
Hearing Decreased	1.1	1.8	1.6
Metabolic and Nutritional Disorders			
Weight Decrease	2.3	7.1	12.6
Musculoskeletal System Disorders			
Myalgia	1.1	1.8	1.2
Platelet, Bleeding and Clotting Disorders			
Epistaxis	1.1	1.8	0.8
Psychiatric Disorders			
Somnolence	10.3	30.1	25.9
Psychomotor Slowing	2.3	16.8	25.1
Nervousness	7.5	15.9	20.6
Difficulty with Memory	2.9	12.4	12.6
Confusion	5.2	9.7	15.0
Depression	6.3	8.0	13.4
Difficulty with Concentration/Attention	1.1	8.0	15.4
Anorexia	4.0	5.3	11.3
Agitation	1.7	4.4	4.0
Mood Problems	1.7	3.5	10.1
Aggressive Reaction	0.6	2.7	4.0
Apathy	0.0	1.8	4.5
Depersonalization	0.6	1.8	1.6
Emotional Lability	1.1	1.8	2.4
Reproductive Disorders, Female	(N=39)	(N=24)	(N=42)
Breast Pain, Female	0.0	8.3	0.0
Dysmenorrhea	2.6	8.3	0.0
Menstrual Disorder	0.0	4.2	0.0
Respiratory System Disorders			
Upper Respiratory Infection	11.5	12.4	12.1
Pharyngitis	2.9	7.1	2.8
Sinusitis	4.0	4.4	4.0
Dyspnea	1.1	1.8	3.2
Skin and Appendages Disorders			
Rash	4.0	4.4	3.2
Pruritus	1.1	1.8	3.2
Sweating Increased	0.0	1.8	0.4
Urinary System Disorders			
Hematuria	0.6	1.8	0.8
Vision Disorders			
Diplopia	6.3	14.2	14.6
Vision Abnormal	2.9	14.2	10.5
Eye Pain	1.1	1.8	2.0
White Cell and Res Disorders			
Leukopenia	0.6	2.7	1.6

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.
[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.
[c] Adverse events reported by at least 1% of patients in the TOPAMAX 200-400 mg/day group and more common than in the placebo group are listed in this table.

Laboratory Tests: There are no known interactions of topiramate with commonly used laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

An increase in urinary bladder tumors was observed in mice given topiramate (20, 75, and 300 mg/kg) in the diet for 21 months. The elevated bladder tumor incidence, which was statistically significant in males and females receiving 300

sures measured in patients receiving topiramate therapy at the recommended human dose (RHD) of 400 and 1.5 to 2 times steady state topiramate exposure in patients receiving 400 mg of topiramate plus phenytoin. The relevance of this finding to human carcinogenic risk is certain. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at

...mutagenic in the Ames test or the *in vitro* mouse ...ma assay; it did not increase unscheduled DNA syn... in rat hepatocytes *in vitro*; and it did not increase ...somal aberrations in human lymphocytes *in vitro* or ...rrow *in vivo*.

...ere observed on male or female fertility were observed ...ses up to 100 mg/kg (2.5 times the RHD on a ... basis).

...ancy: Pregnancy Category C.

...amate has demonstrated selective developmental tox... including teratogenicity, in experimental animal stud... ...when oral doses of 20, 100, or 500 mg/kg were admin... ...to pregnant mice during the period of organogenesis, ...idence of fetal malformations (primarily craniofacial ...cleft) was increased at all doses. The low dose is approx... ...0.2 times the recommended human dose (RHD=400 ...) on a mg/m^2 basis. Fetal body weights and skeletal ...ation were reduced at 500 mg/kg in conjunction with ...decreased maternal body weight gain.

...rat studies (oral doses of 20, 100, and 500 mg/kg or 0.2, ...30 and 400 mg/kg), the frequency of limb malformations ...dactyly, micromelia, and amelia) was increased among ...offspring of dams treated with 400 mg/kg (10 times the ...RHD on a mg/m^2 basis) or greater during the organogenesis ...period of pregnancy. Embryotoxicity (reduced fetal body ...weights, increased incidence of structural variations) was ...observed at doses as low as 20 mg/kg (0.5 times the RHD on ...a mg/m^2 basis). Clinical signs of maternal toxicity were seen ...at 400 mg/kg and above, and maternal body weight gain ...was reduced during treatment with 100 mg/kg or greater.

...rabbit studies (20, 60, and 180 mg/kg or 10, 35, and 120 ...mg/kg orally during organogenesis), embryo/fetal mortality ...was increased at 35 mg/kg (2 times the RHD on a mg/m^2 ...basis) or greater, and teratogenic effects (primarily rib and ...vertebral malformations) were observed at 120 mg/kg (6 ...times the RHD on a mg/m^2 basis). Evidence of maternal tox... (decreased body weight gain, clinical signs, and/or mor...) was seen at 35 mg/kg and above.

...When female rats were treated during the latter part of ges... ...and throughout lactation (0.2, 4, 20, and 100 mg/kg or ...0.20 and 200 mg/kg), offspring exhibited decreased viabil... ...and delayed physical development at 200 mg/kg (5 times ...the RHD on a mg/m^2 basis) and reductions in pre- and/or ...postweaning body weight gain at 2 mg/kg (0.05 times the ...RHD on a mg/m^2 basis) and above. Maternal toxicity (de... ...body weight gain, clinical signs) was evident at 100 ...mg/kg or greater.

...In a rat embryo/fetal development study with a postnatal ...component (0.2, 2.5, 30 or 400 mg/kg during organogenesis; ...listed above), pups exhibited delayed physical development ...at 400 mg/kg (10 times the RHD on a mg/m^2 basis) and per... ...reductions in body weight gain at 30 mg/kg (1 times ...the RHD on a mg/m^2 basis) and higher.

...There are no studies using TOPAMAX® (topiramate) in ...pregnant women. TOPAMAX® should be used during preg... ...only if the potential benefit outweighs the potential ...risk to the fetus.

...In post-marketing experience, cases of hypospadias have ...been reported in male infants exposed in utero to topira... ...with or without other anticonvulsants; however, a ...causal relationship with topiramate has not been estab...

...bor and Delivery:

...In studies of rats where dams were allowed to deliver pups ...naturally, no drug-related effects on gestation length or par... ...were observed at dosage levels up to 200 mg/kg/day. ...The effect of TOPAMAX® (topiramate) on labor and delivery ...in humans is unknown.

...ing Mothers:

...Topiramate is excreted in the milk of lactating rats. It is not ...known if topiramate is excreted in human milk. Since many ...drugs are excreted in human milk, and because the poten... ...for serious adverse reactions in nursing infants to ...TOPAMAX® (topiramate) is unknown, the potential benefit ...to the mother should be weighed against the potential risk ...to the infant when considering recommendations regarding ...nursing.

...tric Use:

...Safety and effectiveness in children have not been estab... ...Use: The pharmacokinetic profile of TOPAMAX® was ...studied in patients between the ages of 4 and 17 years [see ...CLINICAL PHARMACOLOGY; Pediatric Pharmacokinet...

...ric Use:

...In clinical trials, 2% of patients were over 60. No age related ...differences in effectiveness or adverse effects were seen. ...There were no pharmacokinetic differences related to age ...although the possibility of age-associated renal func... ...abnormalities should be considered.

...ex and Gender Effects:

...Evaluation of efficacy and safety in clinical trials has shown ...no sex or gender related effects.

...SE REACTIONS

...The most commonly observed adverse events associated ...with the use of topiramate at dosages of 200 to 400 mg/day ...in controlled trials, that were seen at greater frequency in ...topiramate-treated patients and did not appear to be dose-... ...were: somnolence, dizziness, ataxia, speech disor... ...speech problems, psychomotor slowing, ...and paresthesia [see Table 4]. The most com... ...adverse events at dosages of 200 to 1,000

Table 5: Incidence (%) of Dose-Related Adverse Events From Five Placebo-Controlled, Add-On Trials

Adverse Event	Placebo (N=174)	TOPAMAX® Dosage (mg/day) 200 (N=45)	400 (N=68)	600-1,000 (N=247)
Fatigue	14.4	11.1	11.8	30.8
Nervousness	7.5	13.3	17.6	20.6
Difficulty with Concentration/Attention	1.1	6.7	8.8	15.4
Confusion	5.2	8.9	10.3	15.0
Depression	6.3	8.9	7.4	13.4
Anorexia	4.0	4.4	5.9	11.3
Language problems	0.6	2.2	8.8	11.7
Anxiety	5.2	2.2	2.9	9.3
Mood problems	1.7	0.0	5.9	10.1
Cognitive problems NOS	0.6	0.0	0.0	4.0
Weight decrease	2.3	4.4	8.8	12.6
Tremor	6.3	13.3	8.8	13.8

guage problems, anxiety, mood problems, cognitive problems not otherwise specified, weight decreased, and tremor [see Table 5].

In controlled clinical trials, 11% of patients receiving topiramate 200 to 400 mg/day as adjunctive therapy discontinued due to adverse events. This rate appeared to increase at dosages above 400 mg/day. Adverse events associated with discontinuing therapy included somnolence, dizziness, anxiety, difficulty with concentration or attention, fatigue, and paresthesia and increased at dosages above 400 mg/day.

Approximately 28% of the 1,715 individuals with epilepsy who received topiramate at dosages of 200 to 1,600 mg/day in clinical studies discontinued treatment because of adverse events; an individual patient could have reported more than one adverse event. These adverse events were: psychomotor slowing (4.1%), difficulty with memory (3.3%), fatigue (3.3%), confusion (3.2%), somnolence (3.2%), difficulty with concentration/attention (2.9%), anorexia (2.9%), depression (2.6%), dizziness (2.6%), weight decrease (2.5%), nervousness (2.2%), ataxia (2.2%), paresthesia (2.0%), and language problems (2.0%).

Incidence in Controlled Clinical Trials – Add-On Therapy

Table 4 lists treatment-emergent adverse events that occurred in at least 1% of patients treated with 200 to 400 mg/day topiramate in controlled trials that were numerically more common at this dose than in the patients treated with placebo. In general, most patients who experienced adverse events during the first eight weeks of these trials no longer experienced them by their last visit.

The prescriber should be aware that these data were obtained when TOPAMAX® was added to concurrent antiepileptic drug therapy and cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with data obtained from other clinical investigations involving different treatments, uses, or investigators. Inspection of these frequencies, however, does not provide the prescribing physician with a basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

[See table 4 at top of previous page]

[See table 5 above]

Other Adverse Events Observed

Other events that occurred in more than 1% of patients treated with 200 to 400 mg of topiramate in placebo-controlled trials but with equal or greater frequency in the placebo group were: fatigue, headache, injury, anxiety, rash, pain, convulsions aggravated, coughing, gastroenteritis, rhinitis, back pain, hot flushes, bronchitis, abnormal gait, involuntary muscle contractions, and epistaxis.

Other Adverse Events Observed During All Clinical Trials

Topiramate, initiated as adjunctive therapy, has been administered to 1,715 patients with epilepsy during all clinical studies. During these studies, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified WHOART dictionary terminology. The frequencies presented represent the proportion of 1,715 topiramate-treated patients who experienced an event of the type cited on at least one occasion while receiving topiramate. Reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* occurring in at least 1/100 patients: *infrequent* occurring in 1/100 to 1/1000 patients; *rare* occurring in fewer than 1/1000 patients.

Autonomic Nervous System Disorders: *Infrequent:* vasodilation.

Body as a Whole: *Frequent:* fatigue, fever, malaise. *Infrequent:* syncope, halitosis, abdomen enlarged. *Rare:* alcohol intolerance, substemal chest pain, sudden death.

Cardiovascular Disorders, General: *Infrequent:* hypertension, hypotension, postural hypotension.

Central & Peripheral Nervous System Disorders: *Frequent:* hypokinesia, vertigo, stupor, convulsions grand mal, hyperkinesea, hypertonia. *Infrequent:* leg cramps, hyporeflexia, field defect, coma, encephalopathy, fecal incontinence, upper motor neuron lesion. *Rare:* cerebellar syndrome, EEG abnormal, tongue paralysis.

Endocrine Disorders: *Infrequent:* goiter. *Rare:* thyroid disorder.

Gastrointestinal System Disorders: *Frequent:* diarrhea, vomiting, flatulence, gastroenteritis. *Infrequent:* gum hyperplasia, hemorrhoids, tooth caries, stomatitis, dysphagia, melena, gastritis, saliva increased, hiccough, gastroesophageal reflux, tongue edema, esophagitis. *Rare:* eructation.

Hearing and Vestibular Disorders: *Frequent:* tinnitus. *Rare:* earache, hyperacusis.

Heart Rate and Rhythm Disorders: *Frequent:* palpitation. *Infrequent:* AV block bradycardia, bundle branch block. *Rare:* arrhythmia, arrhythmia atrial, fibrillation atrial.

Liver and Biliary System Disorders: *Infrequent:* SGPT increased, SGOT increased, gall bladder disorder. *Rare:* gamma-GT increased.

Metabolic and Nutritional Disorders: *Frequent:* weight increase. *Infrequent:* thirst, hypokalemia, alkaline phosphatase increased, dehydration, hypocalcemia, hyperlipemia, acidosis, hyperglycemia, creatinine increased, hyperchloremia, xerophthalmia. *Rare:* diabetes mellitus, hypernatremia, abnormal serum folate, hyponatremia, hypocholesterolemia, hypoglycemia, hypophosphatemia.

Musculoskeletal System Disorders: *Frequent:* arthralgia, muscle weakness. *Infrequent:* arthrosis, osteoporosis.

Myo-, Endo-, Pericardial & Valve Disorders: *Infrequent:* angina pectoris.

Neoplasms: *Infrequent:* basal cell carcinoma, thrombocythemia. *Rare:* polycythemia.

Platelet, Bleeding, and Clotting Disorders: *Infrequent:* gingival bleeding, purpura, thrombocytopenia, pulmonary embolism.

Psychiatric Disorders: *Frequent:* insomnia, personality disorder, impotence, hallucination, euphoria, psychosis, libido decreased, suicide attempt. *Infrequent:* paranoid reaction, appetite increased, delusion, paranoia, delirium, abnormal dreaming, neurosis. *Rare:* libido increased, manic reaction.

Red Blood Cell Disorders: *Frequent:* anemia. *Rare:* marrow depression, pancytopenia.

Reproductive Disorders, Female: *Frequent:* intermenstrual bleeding, leukorrhea, menorrhagia, vaginitis, amenorrhea.

Reproductive Disorders, Male: *Infrequent:* ejaculation disorder, breast discharge.

Respiratory System Disorders: *Frequent:* coughing, bronchitis. *Infrequent:* asthma, bronchospasm. *Rare:* laryngismus.

Skin and Appendages Disorders: *Frequent:* acne, alopecia. *Infrequent:* dermatitis, nail disorder, folliculitis, dry skin, urticaria, skin discoloration, eczema, photosensitivity reaction, erythematous rash, seborrhoea, sweating decreased, abnormal hair texture. *Rare:* chloasma.

Special Senses Other, Disorders: *Frequent:* taste perversion. *Infrequent:* taste loss, parosmia.

Urinary System Disorders: *Frequent:* urinary tract infection, micturition frequency, urinary incontinence, dysuria, renal calculus. *Infrequent:* urinary retention, face edema, renal pain, nocturia, albuminuria, polyuria, oliguria.

Vascular (Extracardiac) Disorders: *Infrequent:* flushing, deep vein thrombosis, phlebitis. *Rare:* vasospasm.

Vision Disorders: *Frequent:* conjunctivitis. *Infrequent:* abnormal accommodation, photophobia, abnormal lacrimation, strabismus, color blindness, myopia, mydriasis. *Rare:* cataract, corneal opacity, iritis.

White Cell and Reticuloendothelial System Disorders: *Infrequent:* lymphadenopathy, eosinophilia, lymphopenia, granulocytopenia, lymphocytosis.

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of TOPAMAX® (topiramate) has not been evaluated in human studies.

OVERDOSAGE

In acute TOPAMAX® (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdosage is not recommended. Treatment should be ap-

Topamax—Cont.

propriately supportive. Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, and 1000 mg/day) have not been shown to improve responses.

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy is 400 mg/day in two divided doses. A daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day. It is recommended that therapy be initiated at 50 mg/day followed by titration to an effective dose. Daily doses above 1,600 mg have not been studied.

The recommended titration rate for topiramate is:

	AM DOSE	PM DOSE
Week 1	none	50 mg
Week 2	50 mg	50 mg
Week 3	50 mg	100 mg
Week 4	100 mg	100 mg
Week 5	100 mg	150 mg
Week 6	150 mg	150 mg
Week 7	150 mg	200 mg
Week 8	200 mg	200 mg

It is not necessary to monitor topiramate plasma concentrations to optimize TOPAMAX® therapy. On occasion, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®. Because of the bitter taste, tablets should not be broken.

TOPAMAX® can be taken without regard to meals.

Patients with Renal Impairment:

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis:

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an antiseizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease:

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

HOW SUPPLIED

TOPAMAX® (topiramate) is available as debossed, coated, round tablets in the following strengths and colors:

25 mg white (coded "TOP" on one side; "25" on the other)

100 mg yellow (coded "TOPAMAX" on one side; "100" on the other)

200 mg salmon (coded "TOPAMAX" on one side; "200" on the other)

They are supplied as follows:

25 mg tablets – bottles of 60 count with desiccant (NDC 0045-0639-65)

100 mg tablets – bottles of 60 count with desiccant (NDC 0045-0641-65)

200 mg tablets – bottles of 60 count with desiccant (NDC 0045-0642-65)

TOPAMAX® (topiramate) Tablets should be stored in tightly-closed containers at controlled room temperature, (59 to 86°F, 15 to 30°C). Protect from moisture.

TOPAMAX® (topiramate) is a trademark of OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC.

Raritan, NJ 08869

 Revised February 1999 643-10-443-5

Shown in Product Identification Guide, page 329

TYLENOL® with Codeine ℞

[ti 'len-awl co 'dēn]

(acetaminophen and codeine phosphate tablets and oral solution USP)

Tablets℠ and Elixir℣

Analgesic For Oral Use

No. 3-NSN 6505-00-400-2054—100's

No. 3-NSN 6505-00-147-8347—500's

No. 3-NSN 6505-01-086-2993—U/D 500's

No. 3-NSN 6505-00-372-3032—1000's

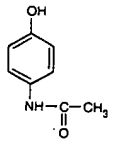
Elixir-NSN 6505-01-035-1963—Pints

No. 3 Codeine Phosphate*	30 mg
Acetaminophen	300 mg
No. 4 Codeine Phosphate*	60 mg
Acetaminophen	300 mg
Each 5 mL of elixir contains:	
Codeine Phosphate*	12 mg
Acetaminophen	120 mg
Alcohol	7%

**Warning* —May be habit forming.

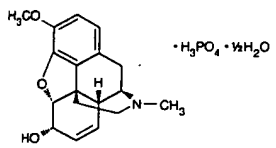
Inactive ingredients: tablets—powdered cellulose, magnesium stearate, sodium metabisulfite†, pregelatinized starch, starch (corn); elixir—alcohol, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, FD&C Yellow No.6.

Acetaminophen, 4 '-hydroxyacetanilide, is a non-opiate, non-salicylate analgesic and antipyretic which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste. Its structure is as follows:



C_8H_9NO M.W. 151.16

Codeine is an alkaloid, obtained from opium or prepared from morphine by methylation. Codeine phosphate occurs as fine, white, needle-shaped crystals, or white, crystalline powder. It is affected by light. Its chemical name is: 7,8-didehydro- 4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. Its structure is as follows:



$C_{18}H_{21}NO_3.H_3PO_4.\ ^1/_2H_2O$ M.W. 406.37

†See WARNINGS

CLINICAL PHARMACOLOGY

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) combine the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen. Both ingredients are well absorbed orally. The plasma elimination half-life ranges from 1 to 4 hours for acetaminophen, and from 2.5 to 3 hours for codeine.

Codeine retains at least one-half of its analgesic activity when administered orally. A reduced first-pass metabolism of codeine by the liver accounts for the greater oral efficacy of codeine when compared to most other morphine-like narcotics. Following absorption, codeine is metabolized by the liver and metabolic products are excreted in the urine. Approximately 10 percent of the administered codeine is demethylated to morphine, which may account for its analgesic activity.

Acetaminophen is distributed throughout most fluids of the body, and is metabolized primarily in the liver. Little unchanged drug is excreted in the urine, but most metabolic products appear in the urine within 24 hours.

INDICATIONS AND USAGE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are indicated for the relief of mild to moderately severe pain.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

TYLENOL with Codeine tablets or elixir (acetaminophen and codeine phosphate tablets and oral solution USP) should not be administered to patients who have previously exhibited hypersensitivity to any component.

WARNINGS

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS

General

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exag-

Acute Abdominal Conditions: The administration of product or other narcotics may obscure the diagnosis ical course of patients with acute abdominal conditions

Special Risk Patients: This drug should be given with tion to certain patients such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Information for Patients

Codeine may impair the mental and/or physical ability quired for the performance of potentially hazardous such as driving a car or operating machinery. The using this drug should be cautioned accordingly.

The patient should understand the single-dose and 24 dose limits, and the time interval between doses.

Drug Interactions

Patients receiving other narcotic analgesics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with this drug may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

The concurrent use of anticholinergics with codeine may produce paralytic ileus.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed with acetaminophen or codeine to determine carcinogenic potential or effects on fertility.

Acetaminophen and codeine have been found to have no mutagenic potential using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study, a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring. There are no studies in humans, and the significance of these findings to humans, if any, is not known.

TYLENOL with Codeine (acetaminophen and codeine phosphate tablets and oral solution USP) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery

Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

Some studies, but not others, have reported detectable amounts of codeine in breast milk. The levels are probably not clinically significant after usual therapeutic dosage. The possibility of clinically important amounts being excreted in breast milk in individuals abusing codeine should be considered.

Pediatric Use

Safe dosage of TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) has not been established in children below the age of three years.

ADVERSE REACTIONS

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain and pruritus.

At higher doses, codeine has most of the disadvantages of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

TYLENOL with Codeine tablets (acetaminophen and codeine phosphate tablets) are a Schedule III controlled substance.

TYLENOL with Codeine elixir (acetaminophen and codeine phosphate oral solution USP) is a Schedule V controlled substance.

Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic